University College London

Vinyl Sulfonates: A Platform for Novel Substrates of Biological Importance

by

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Submitted in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Declaration

I, Oluwabusola Edetanlen-Elliot confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Sulfonamides constitute a vital and diverse class of therapeutic agents. Their means of synthesis has often involved the use of unstable sulfonyl chloride species; however, recent research has established pentafluorophenyl (PFP) and trichlorophenyl (TCP) sulfonate esters as a useful stable alternative to such species.

This thesis describes an exploration into the reactivity of the bifunctional acceptors pentafluorophenyl vinyl sulfonate and trichlorophenyl vinyl sulfonate. Intermolecular alkyl radical addition to trichlorophenol vinyl sulfonate mediated by both 1-ethylpiperidinium phosphate (EPHP) and tributyltin hydride was carried out effectively to generate a library of alkyl sulfonates. Notably, this was extended to the synthesis of a bifunctional alkyl PFP/TCP sulfonate *via* a double radical addition protocol which was envisaged could be useful in determining the reactivity between PFP and TCP.

1,3-Dipolar cycloaddition reactions were carried out effectively at the electron-deficient olefinic portion of the vinylsulfonates to provide functionalized sulfonate esters with excellent regioselectivity. Addition of an α and a β substituent to vinylic portion of PFP and TCP vinyl sulfonate changed the electronics and sterics of the sulfonates, however functionalised esters with great regioselectivity could still be synthesised.

CONTENTS

Acknowledgement

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A big thank you must go to Dr. Abil Aliev for his invaluable help and advice with NMR analysis of my samples, and additionally Dr Lisa Harris for her time and patience in analysing my mass spectrometry samples.

Finally, I could not have gone through my studies without the grace of God and I am forever indebted to my family for their love and support.

Abbreviations

Ac – Acetic

AIBN – 2,2’-azobisisobutyronitrile

AMBN - 2,2'-Azobis-(2-methylbutyronitrile)

Boc – *tert*-Butoxycarbonyl

CA – Carbonic anhydrase

CI – Chemical ionisation

COX – Cyclooxygenase

DABCO – 1,4-Diazabicyclo[2.2.2]octane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM – Dichloromethane

DMAP – Dimethylaminopyridine

DMF – Dimethylformamide

EI – Electron ionisation

EPHP – 1-ethyl piperidinium hypophosphite

ES – Electrospray

Et– Ethyl

FAB – Fast atom bombardment

FMO – Frontier molecular orbital

HOMO – Highest occupied molecular orbital

HRMS – High resolution mass spectrum

Hz – Hertz

IR – Infra-red

LUMO – Lowest unoccupied molecular orbital

Me – Methyl

MP – Melting point

MW – Microwave

NCS – *N*-chlorosuccinimide

NMR – Nuclear magnetic resonance

NSAID – Non-steroidal anti-inflammatory drug

PABA – *para*-Aminobenzoic acid

PFP – Pentafluorophenyl

PFPOH – Pentafluorophenol

Ph – Phenyl

PMB – *para*-Methoxybenzyl

RT – Room temperature

TBAF – *tetra*-Butylammonium fluoride

TCP – 2,4,6-Trichlorophenyl

TCT – 2,4,6-Trichloro-1,3,5-triazine

THF – Tetrahydrofuran

TLC – Thin layer chromatography

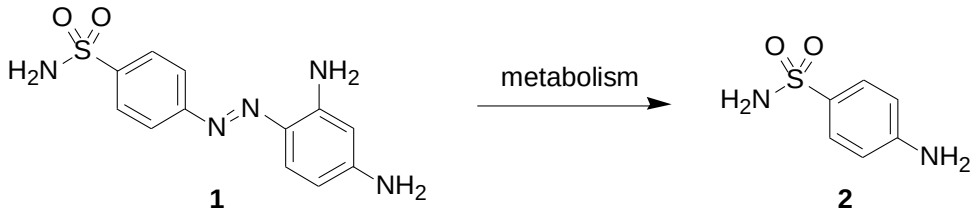
TMS – Trimethylsilyl

UV – Ultra violet

Chapter 1 Introduction

1.1 Sulfonamides as drugs

Sulfonamides have, for many years, been widely studied for their chemotherapeutic activity.[1] Sulfonamide-based medicines were the second antimicrobial drugs and the first effective chemotherapeutic agents to be available in safe therapeutic dosage ranges.[2] They were the mainstay of therapy for bacterial infections in human being before the introduction of penicillin in 1941.[3] The first sulfonamide, trade named Prontosil **1** was first discovered in 1932 although its mode of action was initially not known as it was active *in vivo* but not *in vitro*. However, it was later discovered that the drug was metabolized, releasing the active compound sulfanilamide **2** (Scheme 1).[3-5] The application of sulfonamides has greatly been extended from their primary function as antimicrobial agents, where they act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS) – the key enzyme involved in folate synthesis, to targets such as COX-II inhibitors, loop diuretics, carbonic anhydrase inhibitors and even as an anti-impotence drug.[6]



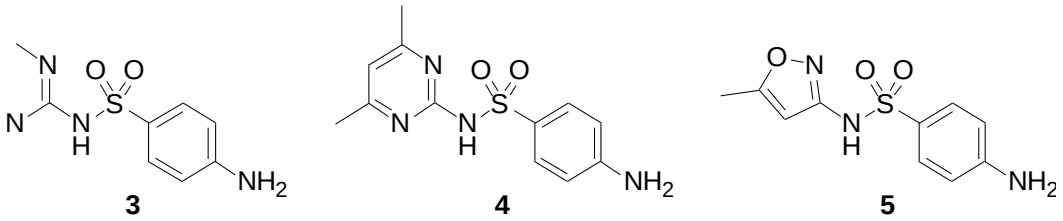
Scheme 1. Metabolism of pro-drug prontosil **1** to sulfanilamide **2**.

1.1.1 Sulfonamides as antibacterial agents

Sulfa drugs were amongst the oldest chemically synthesized antimicrobial agents and are still widely used today for the treatment of various bacterial, protozoal and fungal infections.[1] Sulfanilamide **2** was discovered to be the active entity in microorganisms; it inhibits the synthesis of dihydrofolic acid from *p*-aminobenzoic acid, pteridine, and glutamic acid by inhibition of dihydropteroate synthetase. Dihydropteroate synthetase catalyses the conversion of *p*-aminobenzoate to dihydropteroate, a key step in folate synthesis (Figure 1). Folate is necessary for the cell to synthesize nucleic acids and in its absence cells will be unable to divide.[3]

Figure 1. Biochemical pathway in microorganisms.[7]

Although it was once a very useful antibiotic,[4] the use of sulfanilamide in therapy as a single agent is almost obsolete today due to the development of bacterial resistance to its effects and the development of more effective antimicrobial agents. However, clinical treatment with sulfonamides has undergone a revival with the use of a combination of sulfamethoxazole and trimethoprim to treat urinary tract bacterial infections.[7] In fact, it has been demonstrated that the earlier sulfanilamides such as sulfadiazine **3**, sulfamethazine **4**, and sulfamethoxazole **5** (Figure 2) are better antibacterial agents when used in combination with trimethoprim or its derivatives. This synergistic effect is due to the inhibition of the sequential stages of a common biochemical pathway for the biosynthesis of tetrahydrofolic acid, which is involved in the production of purines (see Figure 1).[1]



3 **4** **5**

Figure 2. Sulfonamide antibacterials sulfadiazine **3**, sulfamethazine **4** and sulfamethoxazole **5**.

1.1.2 Sulfonamides as carbonic anhydrase inhibitors

Carbonic anhydrases (CAs) are ubiquitous metalloenzymes present in prokaryotes and eukaryotes which catalyse the reversible hydration of carbon dioxide to give bicarbonate and a proton:[8]

$$CO_2 + H_2O \rightarrow HCO_3^- + H^+$$

This reaction is involved in many physiological and pathological processes, including: respiration and transport of CO_2 and bicarbonate between metabolizing tissues and lungs, pH and CO_2 homeostasis, electrolyte secretion in various tissues and organs, biosynthetic reactions (such as gluconeogenesis, lipogenesis and ureagenesis), bone resorption, calcification and tumorigenicity.[9,10] Owing to the wide distribution of carbonic anhydrase in its various isoforms throughout the body and its important physiological function, there is a vast number of possible targets for inhibitors, making it an attractive candidate for exploitation.

Carbonic anhydrases, except for CA III, are inhibited primarily by unsubstituted sulfonamides possessing the general formula RSO_2NH_2 (R = aryl, hetaryl, perhaloaryl). For example, acetazolamide **6**, methazolamide **7**, ethoxzolamide **8** and dichlorophenamide **9**, dorzolamide **10** and brinzolamide **11** (Figure 3) have being employed for nearly 45 years as neurological agents and are also used as antiglaucoma/antisecretory drugs.[11]

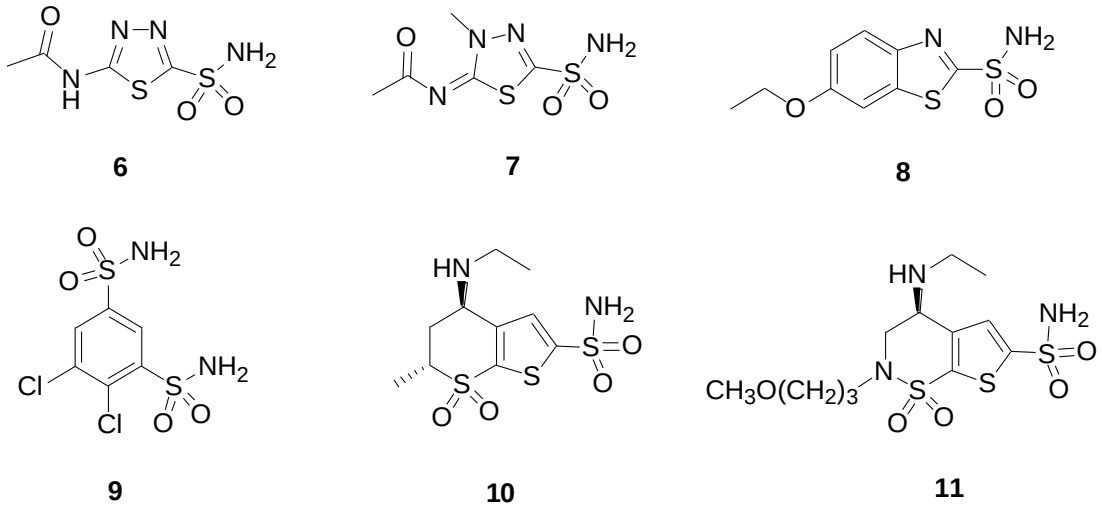


Figure 3. Sulfonamide inhibitors of carbonic anhydrases.

1.1.3 Sulfonamides as COX-II Inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat arthritis, menstrual pain, and headache.[12] NSAIDs exert their major therapeutic and adverse effects by inhibition of cyclooxygenase (COX), a key enzyme for prostanoid synthesis.[12] Although effective, their long-term use is limited by gastrointestinal effects such as dyspepsia and abdominal pain and, less often, gastric or duodenal perforation or bleeding.[12,13] However, the discovery of two COX isoforms, a constitutive COX-1, serving homeostatic prostanoid synthesis, and an inducible COX-2, responsible for proinflammatory prostanoid production, ushered in a new generation of NSAIDs, the coxibs, which selectively inhibit the COX-2 isoforms, reducing adverse effects.[12] Celecoxib **12** and valdecoxib **13** (Figure 4) are sulfonamide-containing COX inhibitors that have been marketed as safe alternatives to NSAIDs for the treatment of pain. However, owing to an increased risk of heart attacks and stroke the first generation coxibs have been superseded by inhibitors such as etoricoxib **16** which promise reduce of further of NSAID-typical adverse effects. The presence of the sulfonamide moiety also makes celecoxib and valdecoxib potent carbonic anhydrase inhibitors (see section 1.1.2).[9]

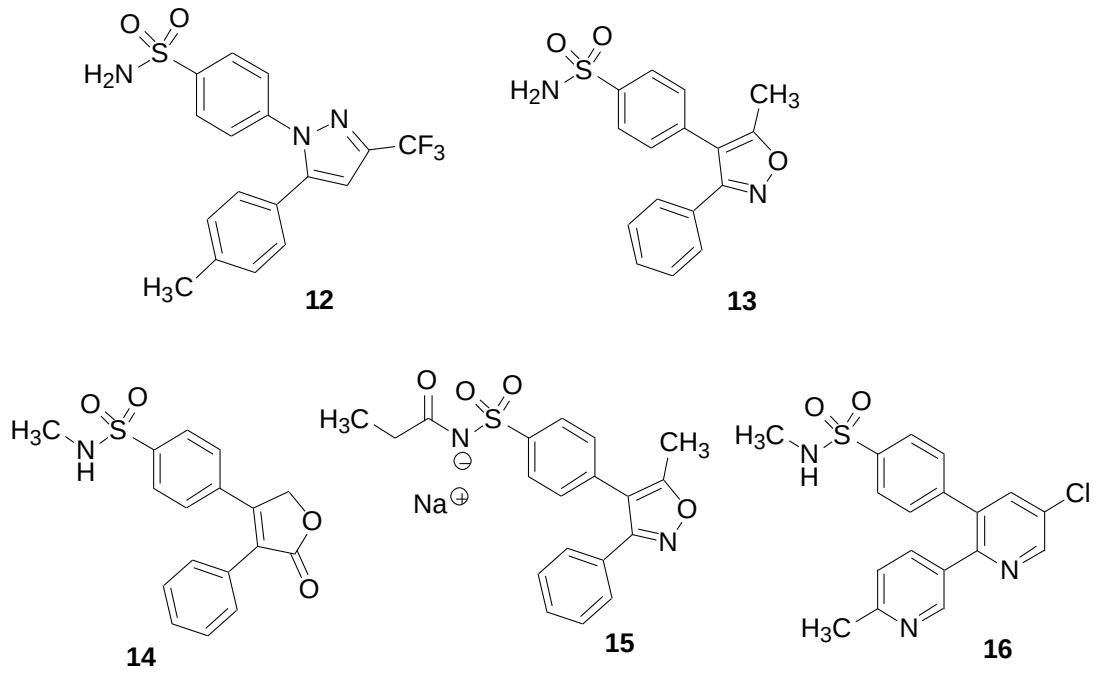
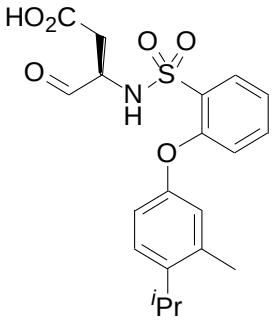


Figure 4. Sulfonamide-based COX-2 inhibitors.

1.1.4 Sulfonamides as cysteine protease inhibitors

Cysteine proteases are an important class of enzymes that selectively catalyze the hydrolysis of peptide bonds. Uncontrolled, unregulated, or undesired proteolysis can lead to many disease states including emphysema, stroke, viral infections, cancer, Alzheimer's disease, inflammation, and arthritis.[14] Cysteine proteases inhibitors thus have considerable therapeutic potential in a variety of disease states.

Caspase-1, also known as interleukin-1β converting enzyme (ICE), was one of the first to be discovered in the family of cysteine proteases.[15] This enzyme is responsible for processing the inactive pro-form of interleukin-1β (1L-1β), a cytokine involved in the pathogenesis of chronic and acute inflammatory disease including arthritis, Alzheimer's disease, and septic shock, into its active form.[16] Thus, inhibition of caspase-1 would modulate the levels of IL-1β, and thus control inflammation. Sharhripour and co-workers have reported diphenyl ether sulfonamide **17** as a potent inhibitor of caspase-1, K_i = 0.1 μM (Figure 5).[16] Fosamprenavir **18**, and its predecessor amprenavir, are HIV protease inhibitors based around a sulfonamide scaffold and have been used successfully in conjunction with reverse transcriptase inhibitors for the treatment of AIDS.[6]



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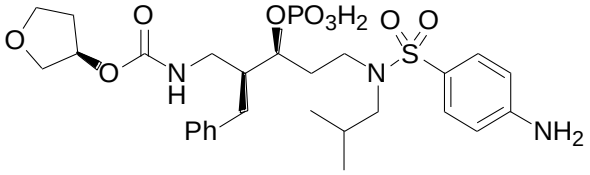

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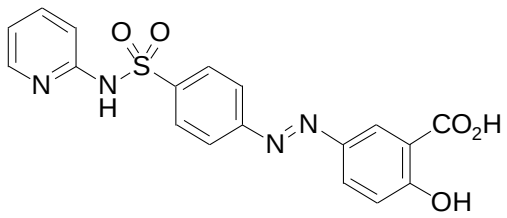
Figure 5. Sulfonamide based protease inhibitors.

1.1.5 Other applications for sulfonamides

Sulfonamides have been employed in the treatment of a plethora of other indications.[17] For example, pyridinyl sulfonamide sulfasalazine (Azulfidine® **19**) has been approved as an anti-inflammatory pro-drug for the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. It is also effective in several types of arthritis, particularly rheumatoid arthritis.[18] One of the most widely used sulfonamide drugs in use today is sildenafil **20**, marketed as Viagra®. It is a drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH) by inhibiting cGMP specific phosphodiesterase type 5, an enzyme that regulates blood flow in the penis.[19] Since becoming available in 1998, sildenafil **20** has been the prime treatment for erectile dysfunction with annual sales of $1.6 billion (US) in the year 2006.[20]



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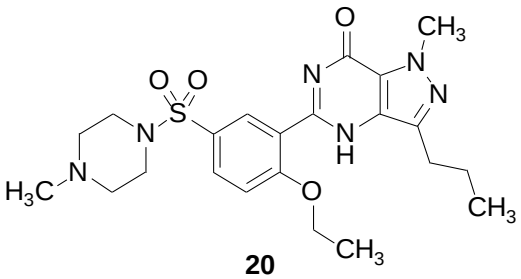

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Figure 6. Sulfonamide containing drugs sulfasalazine **19** and sildenafil **20**.

In conclusion, sulfonamides represent a diverse and relevant class of therapeutic drugs. The sulfonamide group remains a vital motif for the development of more effective drugs to treat an increasing portfolio of diseases. Thus the development of novel methods for the synthesis of sulfonamides has received a great deal of attention.

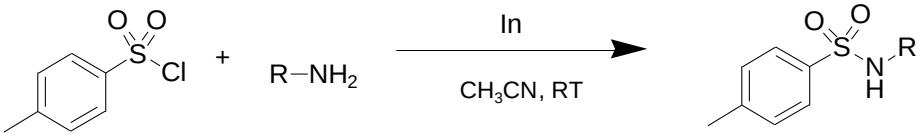
1.2 Synthesis of sulfonamides

Sulfonamides are important pharmaceutical compounds because they exhibit a wide range of biological activities such as anti-cancer, anti-inflammatory and anti-viral functions (see Section 1). Sulfonamides have also been used synthetically as protecting groups of OH or NH functionalities for easy removal under mild conditions.[21] In this section, some pathways for their synthesis are discussed.

1.2.1 Sulfonamides from sulfonyl chlorides

Although many synthetic methods have been currently being reported, sulfonylation of amines with sulfonyl chlorides in the presence of a base is still the most commonly employed method for the synthesis of sulfonamides.[22,23]

An example of sulfonamide synthesis involves the reaction of sulfonyl chlorides using indium catalysis (Scheme 2).[22] Indium metal was used because of its stability in air at ambient temperature, and also because of its low toxicity. Various reaction conditions were evaluated and it was discovered that the reaction was only successful when a catalytic amount of indium metal was used. The authors proposed that the indium metal reacted with sulfonyl chloride to generate electrophilic species, $RSO_2^+InCl^-$, which then undergoes reaction with amines, regenerating the active indium metal along with the corresponding sulfonamide products and HCl.



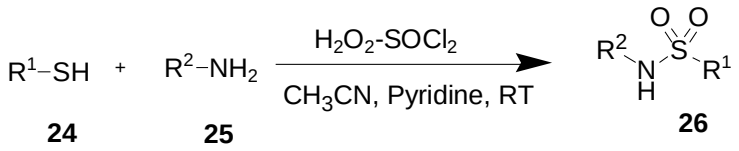
21 **22** **23**

23a: R = Cy, 84%; **23b**: R = Bu, 89%;
23c: R = Ph, 82%; **23d**: R = Bn, 87%

Scheme 2. Sulfonamides from sulfonyl chlorides using indium catalysis.

Another example of sulfonamide synthesis from sulfonyl chlorides that are derived from the direct oxidation of thiols using thionyl chloride and hydrogen peroxide was described by Bahrami *et al.* (Scheme 3).[24] The synthesis used thionyl chloride combined with hydrogen peroxide (H_2O_2) as an inexpensive oxidant for the oxidative chlorination of thiol derivatives **24** to the corresponding sulfonyl chlorides. After the

formation of the sulfonyl chloride *in situ* and upon addition of amines **25**, the corresponding sulfonamides **26** are generated. The reaction proceeds in high yields, 96-98%, and with short reaction times. The reaction also tolerated a variety of substrates bearing either electron-donating or electron-withdrawing substituents.



24 **25** **26**

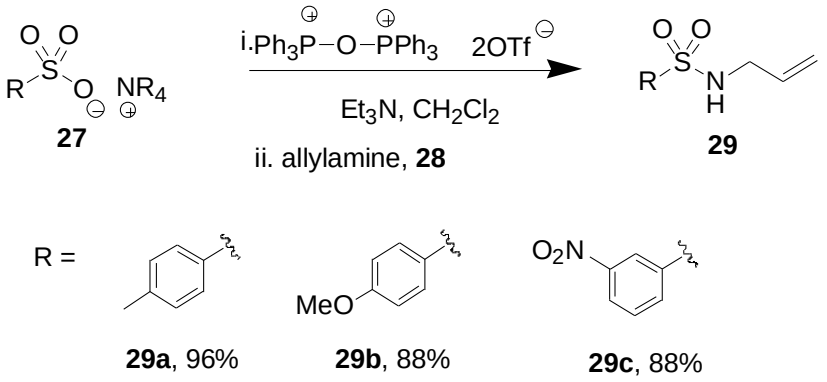
26a: R^1, R^2 = Ph, 97% **26c**: R^1 = Ph, R^2 = PhMe, 96%

26b: R^1 = PhMe, R^2 = Cy, 98% **26d**: R^1 = PhMe, R^2 = NH_3, 97%

Scheme 3. Sulfonamides from oxidation of thiols.

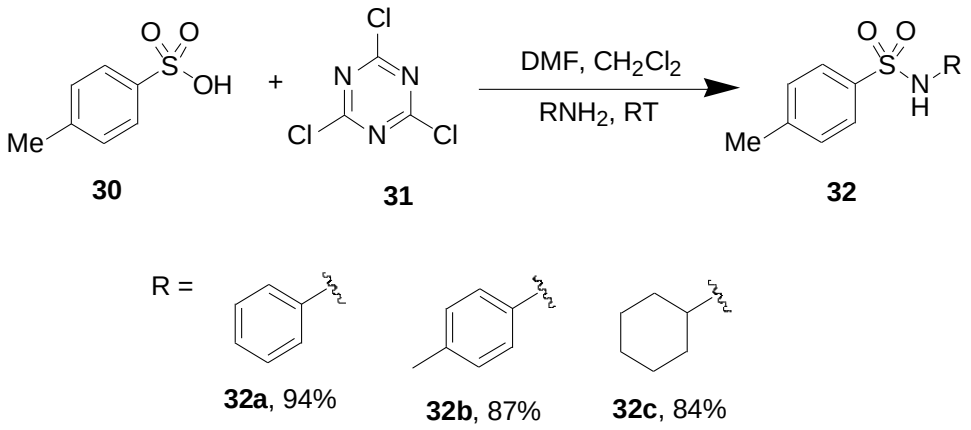
1.2.2 Sulfonamides from sulfonic acids

Sulfonamides can also be synthesised directly from sulfonic acids but there are only a small number of methods available. The first direct route was reported by Caddick *et al*.[25] Here sulfonic acid salts were activated by triphenylphosphine ditriflate and transformed directly to the corresponding sulfonamides or sulfonate ester. Triphenylphosphine ditriflate was chosen in the reaction as reagent as it was envisaged that reaction with sulfonic acids would generate an intermediate that was suitably activated towards nucleophiles. The reaction proved to be successful with a variety of substrates being tolerated and excellent yields achieved. It was also found that the counter ion of the sulfonic acid salt was important as metal salts of sulfonic acid were less soluble and hygroscopic. Substitution of triphenylphosphine oxide for polystyrene-supported phosphine oxide obviated any problems of triphenylphosphine removal, as the reaction products could be removed by washing the filtrate with water.



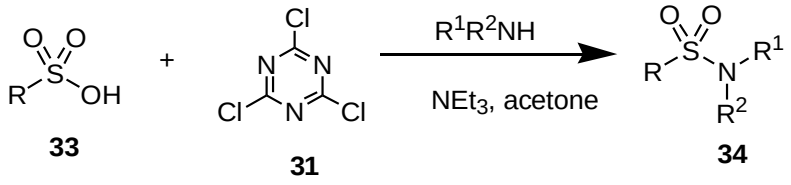
Scheme 4. First synthesis of sulfonamides from sulfonic acid salt.

Another strategy employed by Pandit and co-workers involved a one-pot procedure to synthesise sulfonamides from sulfonic acids and amines using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) **31** and *N*,*N*-dimethylformamide (DMF) at room temperature (Scheme 5).[26] The cyanuric chloride **31** and DMF were complexed together at room temperature after which the sulfonic acid **30** and amine were added to afford the sulfonamides. Primary, secondary, alkyl, aryl and cyclic amines are all tolerated in this reaction and gave excellent yields of sulfonamides **32**.



Scheme 5. Sulfonamide synthesis using cyanuric chloride at RT

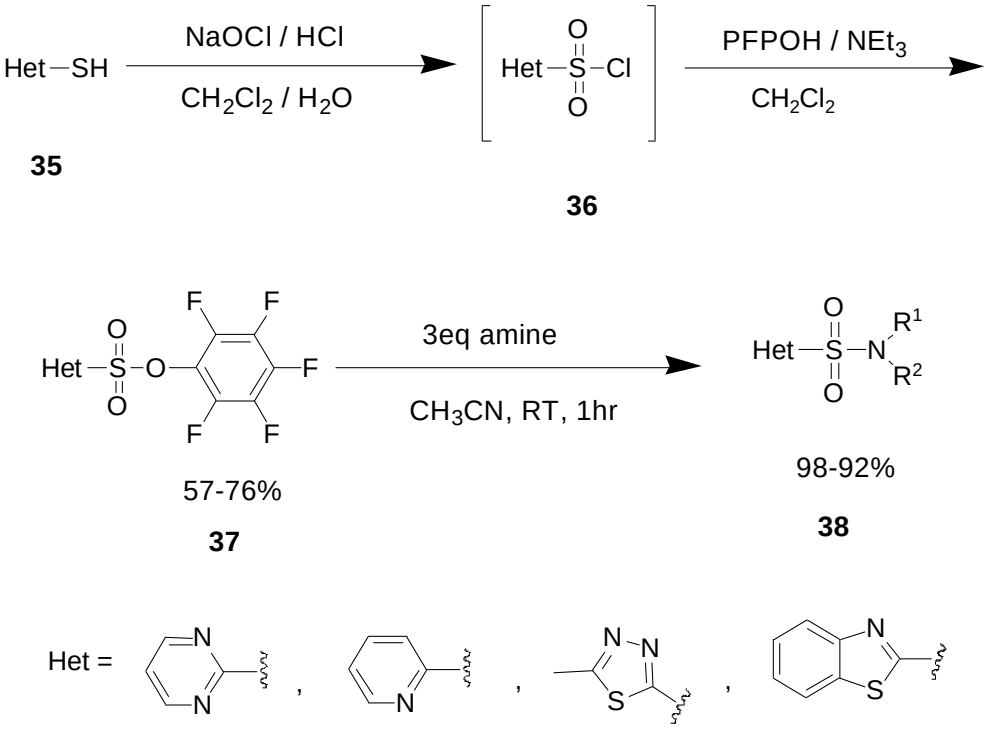
Another example which also employs TCT but under microwave conditions was reported by De Luca *et al.* (Scheme 6).[27] By addition of TCT to a mixture of sulfonic acid and NEt_3 in acetone and utilising microwave irridation, the authors were able to reduce the reaction time from 20 hours to 20 mins.



Scheme 6. Sulfonamide synthesis using cyanuric chloride at MW

1.2.3 Sulfonamides from sulfonate esters

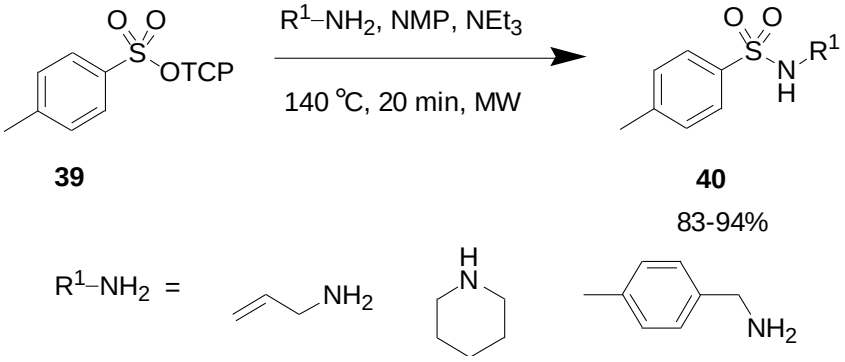
Sulfonamides can also be synthesised from sulfonate esters; this is not an approach that has gained widespread use but an example that uses this method was reported by Bornholdt *et al.*[28] Here they employed pentafluorophenol sulfonate esters to synthesise heterocyclic sulfonamides (Scheme 7). Addition of the thiols **35** to a NaOCl/HCl/CH_2Cl_2 mixture generated the heterocyclic sulfonyl chlorides **36**, which were directly converted to the corresponding heterocyclic PFP sulfonate esters **37**. Subsequent treatment of PFP sulfonate esters **37** with slight excess of either primary or secondary amines in CH_3CN at RT afforded sulfonamides **38**.



Scheme 7. Sulfonamides from heterocyclic PFP sulfonate esters **37**.

Wilden *et al.* have also reported synthesis of sulfonamides using TCP sulfonate ester **39**, a new class of activated sulfonate esters. The authors report that the TCP leaving group was displaced effectively by amines and the reaction was faster using

microwave irridation (Scheme 8). This reaction was tolerant to simple nucleophilic amines as well as challenging amines for example anilines and hindered amines.



Scheme 8. Sulfonamides from TCP sulfonate esters **39**.

To conclude, synthesis of sulfonamides still relies heavily on the use of sulfonyl chlorides or a sulfonyl chloride intermediate which can be trapped by an amine. Some sulfonyl chlorides are difficult to prepare or unstable and are not amenable to long term storage. As sulfonamides are important in medicinal chemistry, research into new ways of synthesising them continues to be an important problem in organic synthesis.

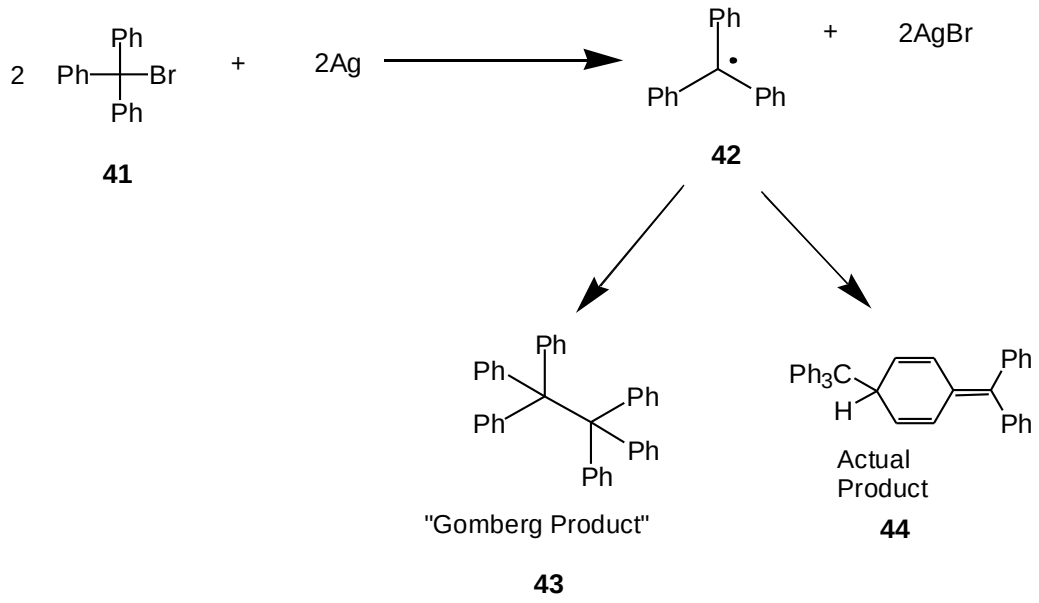
1.3 Radicals and their importance

Initially thought of as a mere 'chemical curiosity', free radical reactions have now become a powerful tool for preparative organic synthesis.[29] Radical chemistry shows numerous advantages over its ionic counterpart, including greater functional-group tolerance, the frequent use of neutral conditions and a capability to be incorporated into elaborate reaction cascades that rapidly increase molecular complexity. Furthermore, radical methodology is amenable to 'green' chemistry as more examples of reactions being performed in water and with a variety of cheap, environmentally benign reagents are being reported.[29,30]

1.3.1 Discovery and development of radical chemistry

The first significant study of free-radical chemistry was described by Gomberg in 1900 when he investigated the reaction of triphenylmethyl bromide **41** with silver (Scheme 9).[31] In the absence of oxygen, the reaction yielded a highly reactive solid which Gomberg proposed to be compound **43**. When in solution, this product existed

in equilibrium with triphenylmethyl radical **42** which was observed to be quite stable. By 1911, there was enough experimental evidence to prove the existence of radical **42** and that the isolated product obtained in the reaction was compound **44**.



Scheme 9. First observation of radicals.

Formation of less stable and more reactive radicals followed, but it was not until 1937 that radicals were postulated to be intermediates in a variety of chemical reactions. A lot of work continued in this area and by 1970 a number of important radical reactions had been developed and numerous targets were prepared using radical chemistry. An increasing understanding of the kinetic and the structural information paved the way for the development of modern synthetic radical chemistry and by 1980, mainstream organic synthesis started to use it routinely in the form of the tin hydride methodology.[31]

1.3.2 Radical initiators

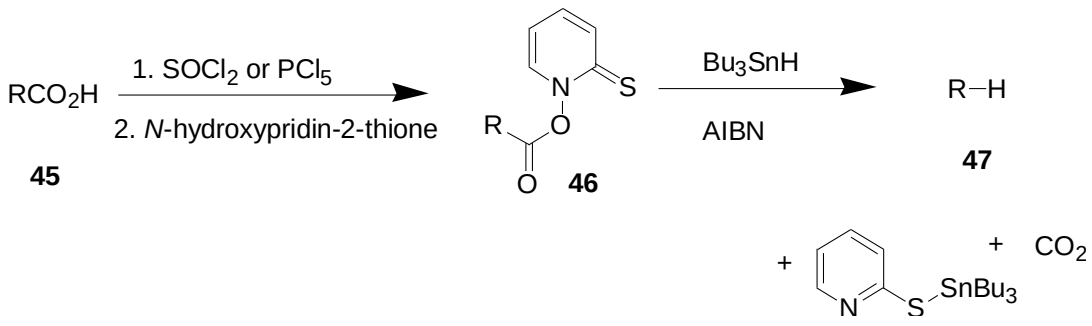
Radical initiators are substances that can produce radical species under mild conditions and promote radical polymerization reactions.[32] Radical reactions are initiated using thermal or photochemical activation to promote homolysis of a weak bond. Although some radical chain processes can occur spontaneously at moderate temperatures, it is usually desirable to facilitate the chain initiation process by deliberate addition of an initiator. Initiators generally possess weak bonds i.e. those with small bond dissociation energies. Typical examples include halogen molecules, azo compounds, and organic peroxides.[30,33]

1.3.3 Radical chain carriers

1.3.3.1 Organotin Reagents

Organotin reagents have been central to the development of modern free-radical chemistry and their use still underpins many endeavours in this field.[29] To date, most radical reactions are conducted using tin hydrides (Bu_3SnH, Me_3SnH, and Ph_3SnH) with the reactions using tributyltin hydride being some of the most powerful and widely applied.[29,31]

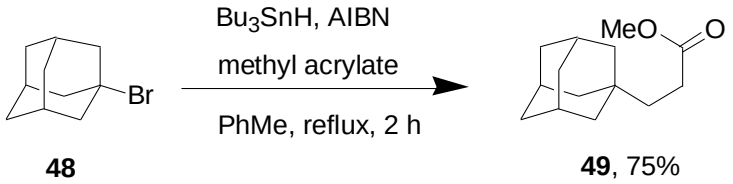
In 1983, Barton *et al.* reported the synthesis of thiohydroxamate ester **46** from carboxylic acid **45**, which on reacting with tributyltin hydride gave the acid decarboxylation product **47**. These esters **46** became known as the Barton esters and formed the general method known as the Barton decarboxylation method.[34]



Scheme 10. Barton decarboxylation method.

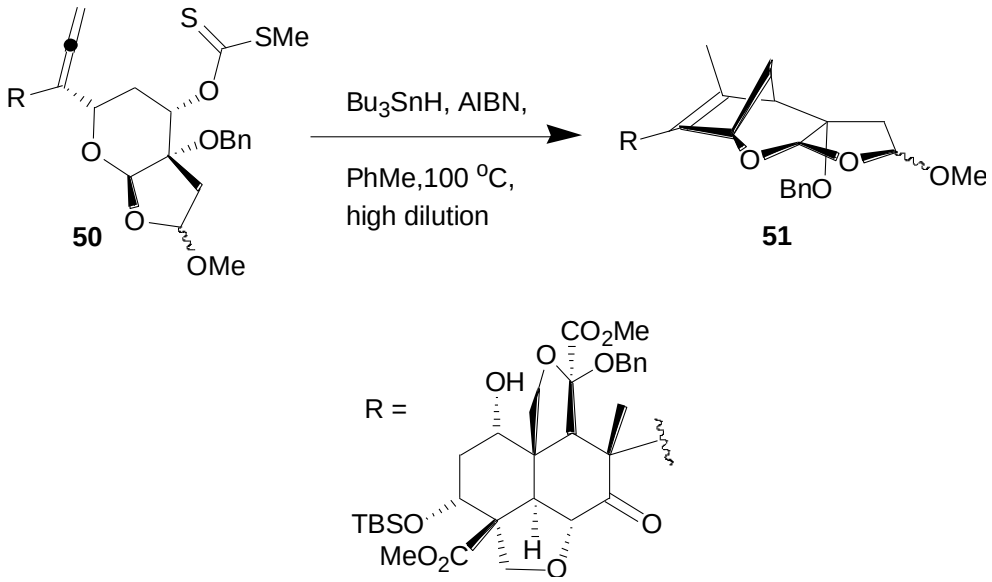
Shuto *et al.* also employed the Barton reductive radical decarboxylation as a key step in the enantioselective synthesis of haloperidol analogue. They found that even though the reaction went quite smoothly with tributyltin hydride as the hydrogen donor, the selectivity was quite poor.[35]

In 2008, Nicolaou *et al.* reported the total synthesis of adamantaplatensimycin with the onset of the synthesis employing a simple radical conjugate addition.[36] Commercially available bromoadamantane **48** was added to methyl acrylate using tributyl tin hydride mediated by AIBN to afford the corresponding adamantyl methyl ester **49** in a 75% yield (Scheme 11).



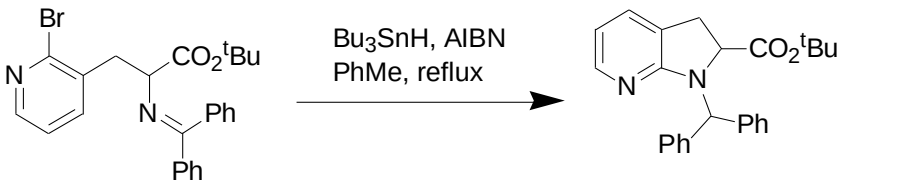
Scheme 11. Synthesis of adamantyl methyl ester **49**.

In 2007, Ley *et al.* reported the total synthesis of azadirachtin[37] using a variation of the Barton-McCombie reaction[38] as one of their key steps (Scheme 12). This radical cyclisation allowed the generation of the tetrasubstitued alkene **51** which upon selective epoxidation provided their target compound. The cyclisation also only yielded the desired endo-alkene which the authors suggest was as a result of the steric inaccessibility of the tertiary radical formed from an alternative *exo* attack. Hence radical trapping with Bu_3SnH had only been possible from the methyl radical formed from the *endo* attack.



Scheme 12. Towards the synthesis of azadirachtin.

Johnston *et al.* reported the synthesis of two non-natural proline derivatives: (*S*)- and (*R*)-7-azaindoline-aminoacetate **53**, using radical cyclisation of (*S*)- and (*R*)-2-(benzhydrylidene-amino)-3-(2-bromopyridin-3-yl)-propionic acid *tert*-butyl ester **52**.[39]

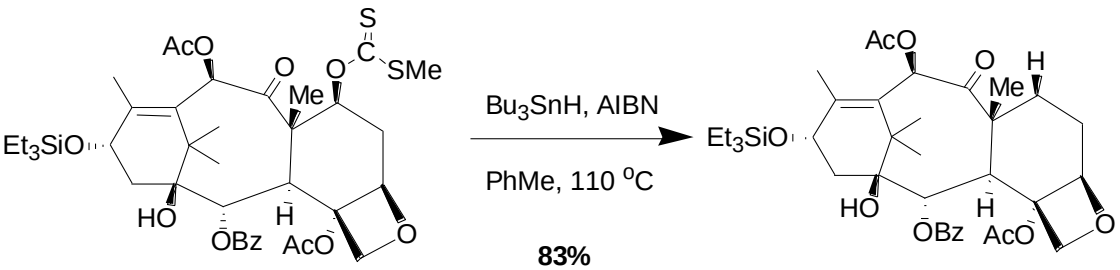


52

53:(*S*) = >99% ee (53%)
53:(*R*) = >99% ee (67%)

Scheme 13. Synthesis of non-natural proline derivatives **53**.

Chen *et al.* were also able to show the synthetic utility of organotin chemistry in their synthesis of 7-deoxytaxol where xanthate **54** was chemoselectively reduced to give the 7-deoxy analogue **55** in an excellent yield (Scheme 14).[40]



54 **55**

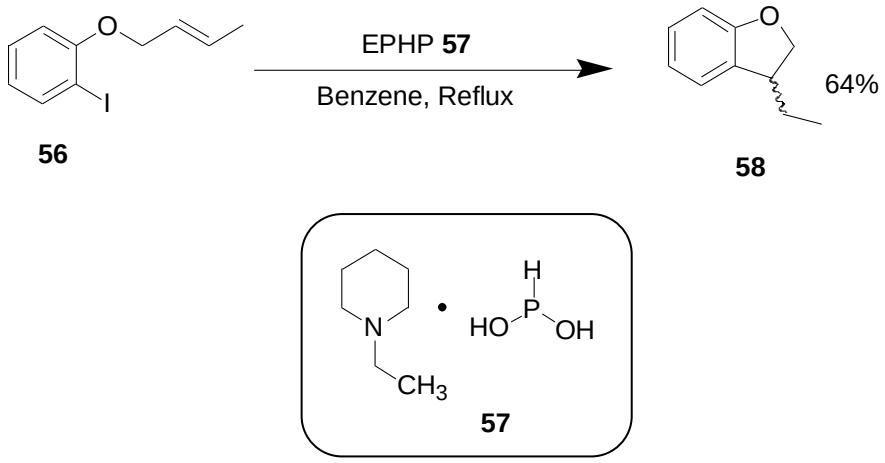
Scheme 14. Towards the synthesis of 7-deoxytaxol.

The use of organotin compounds is still widespread in free-radical chemistry; however there are several problems associated with these compounds. Organotin compounds are toxic (which creates a disposal problem), the formation of tin residues often makes workup and product isolation difficult and the experimental procedure often requires slow addition of the tri-*n*-butyltin hydride over several hours in order to keep its concentration low. However as these reactions are important in organic synthesis, a number of methods have been developed to ameliorate these limitations. These include: development of various workup procedures for reactions involving stoichiometric R_3SnH,[41] use of catalytic amounts of a tin hydride or its precursor and stoichiometric amounts of another hydride (for example $NaBH_4$,[42] or $NaCNBH_3$[43]), use of modified stannanes including fluorous stannanes,[44,45] and use of solid-supported stannanes.[29] Also, the use of alternatives to stannanes, especially silanes, dialkyl phosphites and hypophosphorous acid has received a great deal of attention.[45]

1.3.3.2 Non-tin reagents

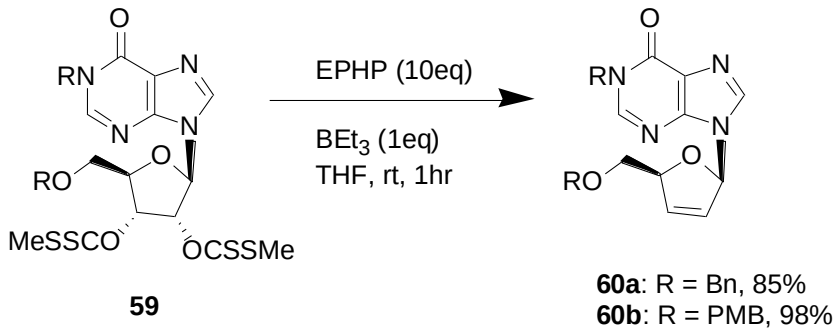
1.3.3.2.1 Organophosphorus reagents

Phosphorus reagents show considerable promise as a substitute for traditional tin hydrides. Their attraction arises from their relatively low cost, reduced toxicity and ease of removal.[29] One of the most commonly employed phosphorus reagent is the salt 1-ethylpiperidinium hypophosphite (EPHP) **57**, which was first applied to radical C-C bond forming reactions by Graham *et al*.[46] They were able to show that EPHP could be used in radical cyclisations onto various alkene side-chain units of both aryl iodide and alkyl bromide substrates such as **56** to generate the cyclised product **58** in a 64% yield (Scheme 15).



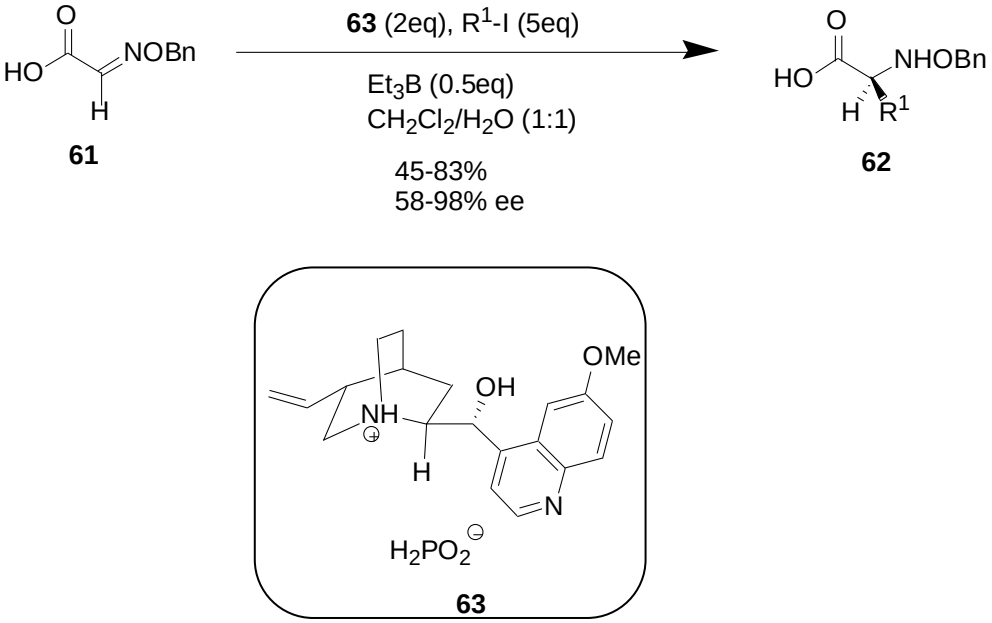
Scheme 15. Use of EPHP in radical cyclisation.

Using 1-ethylpiperidinium hypophosphite (EPHP) **57** as a radical reducing agent, Torii *et al.* have reported deoxygenation of nucleosides in the their synthesis of 2,3-dideoxyinosine.[47] Deoxygenation of bisxanthate **59** to alkene **60** was readily achieved in an excellent yield. In contrast to the case of tin reduction, the isolation and purification of alkene **60** was efficient because there was no metal contamination (Scheme 16).



Scheme 16. Towards the synthesis of 2,3-dideoxyinosine.

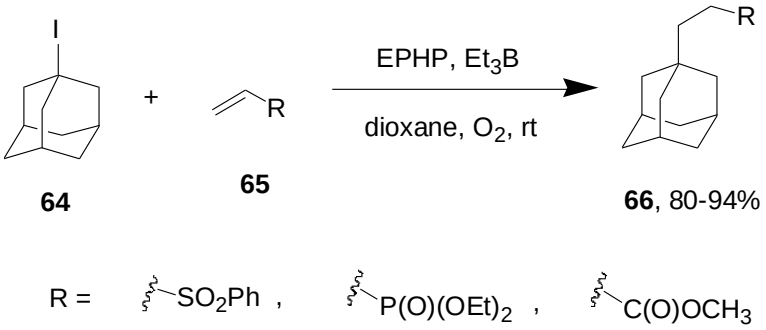
An attractive feature of phosphorus based reagents is their water solubility. However, whilst the radical-chain carrier, EPHP hypophosphite, is water-soluble, many organic compounds are not and, as a result if the reaction is to be carried out in aqueous media, it is often crucial that a surfactant or phase-transfer reagent is added.[29] Jang *et al.*[48] were able to combine this water solubility feature of EPHP with the enantioselective synthesis in their chemistry (Scheme 17). In this reaction, hypophosphite salt **63** acts as the radical-chain carrier, surfactant and chiral additive, capable of inducing high enantioselectivity (up to 98% ee). The optimum reaction medium comprised a mixture of dichloromethane and water, with pure water or pure dichloromethane resulting in greatly reduced yield.



Scheme 17. Use of hypophosphite salt in aqueous medium.

The use of EPHP radical chain carrier in intermolecular carbon-carbon bond formation was reported by Jang *et al.*[49] Using 1-adamantyl iodide **64** as a model

compound, the authors were able to carry out intermolecular addition to various alkenes **65** under mild reaction condition with great success (Scheme 18).

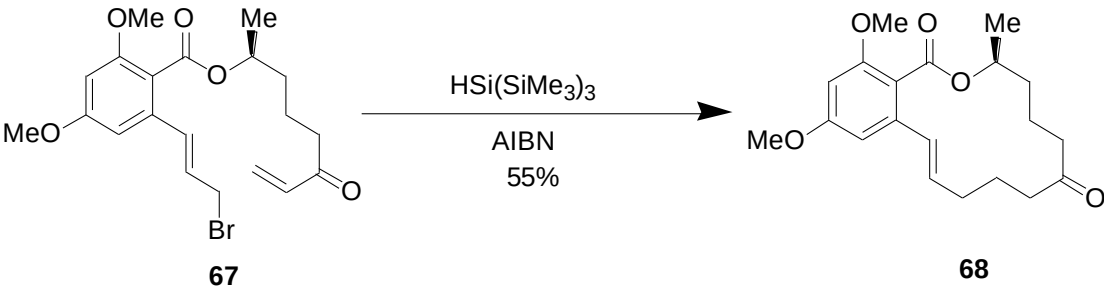


Scheme 18. EPHP in intermolecular reactions.

The use of phosphorus-based radical reagents should continue to gain wider acceptance as the reagents are cheaper, less toxic and more readily removed than their tin counterparts. Their use in aqueous reaction media also makes them even more attractive especially as environmental considerations become more important.

1.3.3.2.2 Organosilane reagents

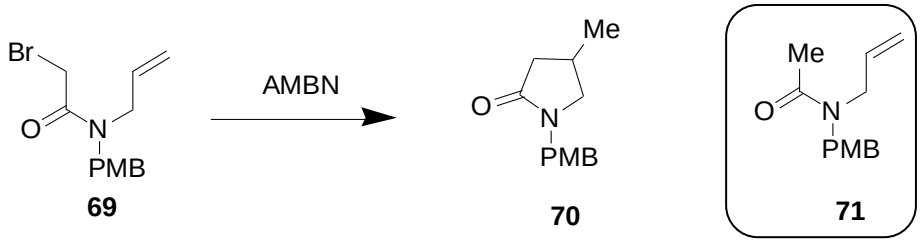
Organosilanes have been a popular alternative to tin hydrides for nearly twenty years.[50] Compared to tin hydrides, organosilanes are less effective hydrogen-atom donors and this makes them ideal reagents for reactions that are plagued by premature reduction.[51] Hitchcock *et al.* reported the synthesis of (–)-zearalenone, a 14-membered ring macrocycle,[52] utilising tris(trimethylsilyl)silane as the radical donor. When bromide **67** was treated with tris(trimethylsilyl)silane and AIBN under high dilution in toluene at 85 °C, it underwent a clean 14-*endo*-trig cyclisation to (*S*)-(+)-zearalenone dimethyl ether **68**, which was produced as a white crystalline solid in 55% yield.



Scheme 19. Synthesis of (–)-zearalenone **68**.

1.3.3.2.3 Germanium hydrides

Triorganogermanes are also potential replacements for organotin reagents. They are perceived to be less harmful than tin hydrides, although full toxicology studies have yet to be performed. The two most common germanium hydrides used are tributylgermanium hydride and tri-(2-furyl) germanium hydride.[29] Tributylgermanium hydride is readily prepared in one step from germanium (IV) chloride and is also commercially available. One advantage of tributylgermanium hydride over its organotin equivalent can be seen in the cyclisation of amide **69** to lactam **70** as when organotin is used there is premature reduction to produce compound **71** (Scheme 20).[29] Further uses of germanium hydrides that have been reported include the reduction of bromides[53] and aromatic azides to amines.[54]



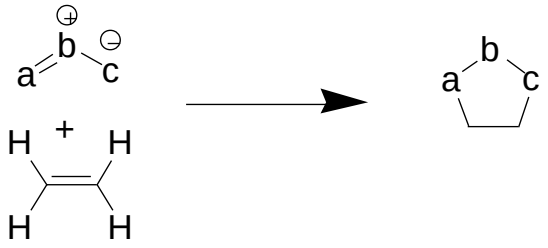
Bu_3SnH (1.4eq), 0.5h; **70** = 39%, **71** = 33%
Bu_3GeH (1.1eq), 5.5h; **70** = 64%, **71** = 8%

Scheme 20. Germanium hydrides in radical cyclisation.

In conclusion, there is considerable utilisation of free radical chemistry in modern organic synthesis. For free radical reactions to be truly useful in organic synthesis it must be chemo-, regio-, diastereo-, and/or enantio selective. By due consideration of reagents, solvents, etc., it is quite possible, in most synthetic routes, to devise a radical process that is capable of effecting a highly selective transformation.

1.4 1,3-Dipolar cycloaddition with nitrones

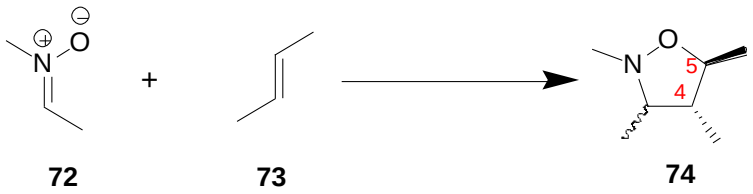
The 1,3-dipolar cycloaddition reaction, also known as the Huisgen cycloaddition or Huisgen reaction, is an extremely powerful, yet mild, means of producing carbon-carbon bonds as well as carbon-oxygen and carbon-nitrogen bonds.[55-58] The ring constructive power of this reaction is now well appreciated and has been employed by numerous groups in the total synthesis of alkaloids and other nitrogen-containing natural products.[59] The reactants of these cycloadditions are a 1,3-dipole and a dipolarophile, often a substituted alkene (Scheme 21).



Scheme 21. Cycloaddition between a 1,3-dipole and a dipolarophile.

1.4.1 Selectivity in the 1,3-dipolar cycloaddition of nitrones with alkenes

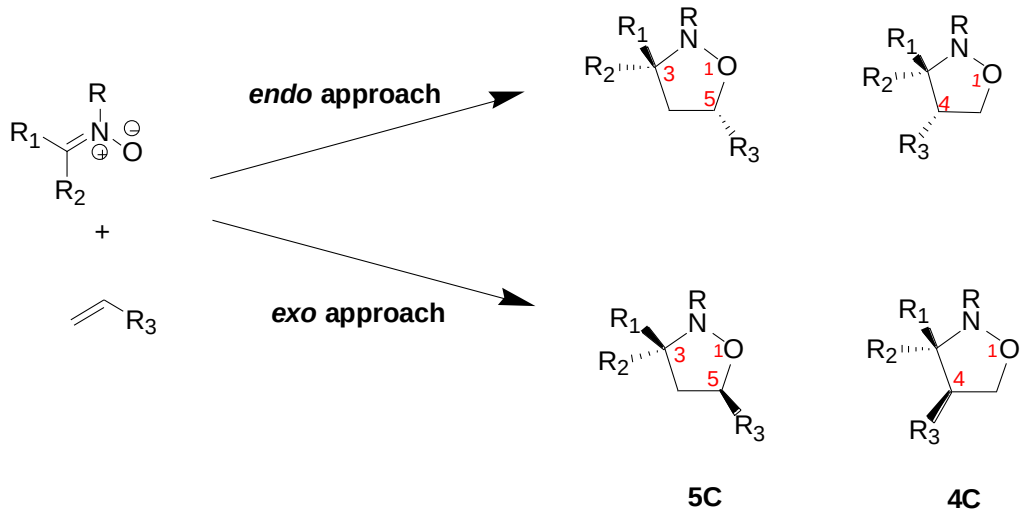
The 1,3-dipolar cycloaddition reaction of nitrones with alkenes gives isoxazolidines. In this reaction, three contiguous chiral centres can be formed as shown in the reaction between nitrone **72** and 1,2-disubstituted alkene **73** (Scheme 22).[56] The relative stereochemistry at C-4 and C-5 is always controlled by the geometric relationship of the substituents on the alkene.



72 **73** **74**

Scheme 22. Formation of chiral isoxazolidines.

The 1,3-dipolar cycloaddition of nitrones with substituted alkenes shows varying degrees of regio- and stereo-selectivity depending on the electronic and steric effects of the substituents. With normal and electron-rich monosubstituted alkenes, the cycloadditions result in the regiospecific formation of 5C-isoxazolidines. However, with electron-deficient alkenes, usually a regioisomeric mixture of adducts are obtained, and in some cases complete reversal in the regioselectivity is observed leading to the isolation of 4C-isoxazolidines as the sole products.[60] The nitrone can also approach the alkene in an *endo* or *exo* attack resulting in two possible diastereoisomers (Scheme 23).

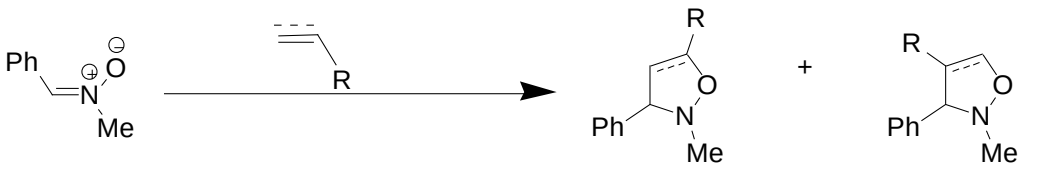


Scheme 23. Formation of 5C- and 4C- regioisomers.

While the frontier molecular orbital treatment is remarkably successful in explaining the regioselectivity and reactivity phenomena,[61] the secondary orbital interactions and steric factors usually dictate the stereochemical outcome of these cycloadditions.[55,56]

1.4.1.1 1,3-Dipolar cycloaddition with electron deficient alkenes

Before FMO theory, the regioselectivity of 1,3-dipolar cycloadditions had perplexed many workers in the field. This was because the regioselectivity for nitrone cycloadditions onto monosubstituted ethylenes was originally believed to proceed in a unidirectional fashion, giving 5-substituted adducts regardless of the alkene substituent.[62] However, using the frontier orbital method to rationalize the effect of substituents on rates and regioselectivity of 1,3-dipolar cycloadditions, Houk *et al.* predicted and proved that a unidirectional addition to both electron-rich and electron-deficient monosubstituted dipolarophiles would no longer be observed when the dipolarophile is made highly electron deficient.[63] His work showed that when mono-substituted electron-deficient dipolarophiles such as phenyl vinyl sulfone, nitroethylene and cyanoacetylene, reversal to give the 4C-substituted cycloadduct **76** as the major product occurred (Scheme 24).



114a

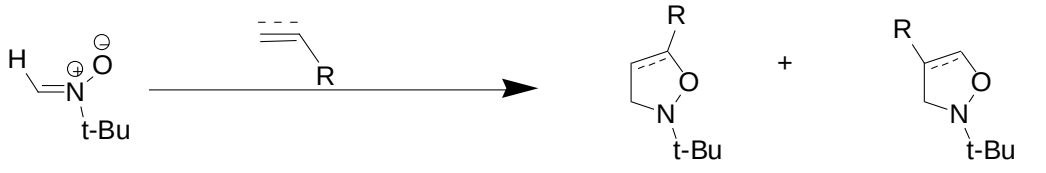
75, 5C

76, 4C

R	**75:76**
CN	0:100
NO_2	0:100
SO_2Ph	32:68

Scheme 24. 1,3-dipolar cycloaddition with electron deficient dipolarophiles.

They also showed that on increasing the steric bulk around the nitrone nitrogen, it was possible to switch the regiospecificity to the 5C cycloadduct **77** irrespective of the electron deficient character of the dipolarophile (Scheme 25).



84

77, 5C

78, 4C

R	**77:78**
CN	50:50
NO_2	100:0
SO_2Ph	70:30

Scheme 25. 1,3-dipolar cycloaddition with bulky substituents on nitrone.

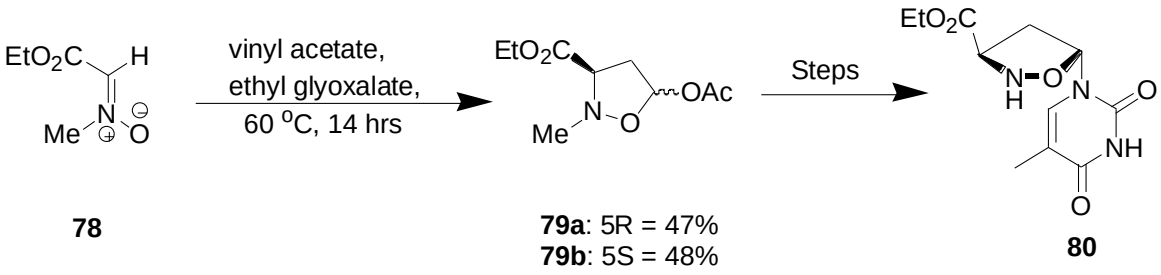
Padwa *et al.* also found that electron deficient nitroethylene reacts readily with *N*-methyl nitrone to give a mixture of *cis* and *trans* 4C-substituted isoxazolines.[55]

1.4.2 Nitrone 1,3-Dipolar cycloaddition in synthesis

As previously noted, the 1,3-dipolar cycloaddition of a nitrone with an olefin is an extremely powerful, yet mild, means of producing carbon-carbon bonds as well as carbon-oxygen and carbon-nitrogen bonds.[56] The powerful nature of this reaction is now well appreciated and numerous natural and unnatural products have been prepared by synthetic routes that have a 1,3-dipolar cycloaddition as a crucial step in their synthesis. Additionally, the potential for control of the contiguous stereocentres in these heterocycles affords additional synthetic opportunities. Consequently, this

reaction has become recognized as an extremely important transformation in the repertoire of the synthetic organic chemist.

1,3-Dipolar cycloaddition have been used for the synthesis of nucleosides, and potent antibiotic and antiviral agents.[64] An example of this is provided by Chiacchio *et al.* in their synthesis of isoxazolidinylthymines **80**.[65] Here, a variety of *C*-functionalised chiral nitrones were used to enforce enantioselection in their cycloaddition with vinyl acetate. It was observed that asymmetric induction was modest when using dipoles whose chiral auxiliary does not maintain a fixed geometry and so cannot completely direct the addition to the nitrone. After poor results with menthol ester and methyl lactate-based nitrones, they were able to prepare and separate isoxazolidine **79a** and its diastereomer **79b** using the *N*-glycosyl nitrone **78**, derived from D-ribofuranose. Adduct **79a** was coupled with thymine before removal of the sugar auxiliary to afford *N*,*O*-nucleoside **80**.



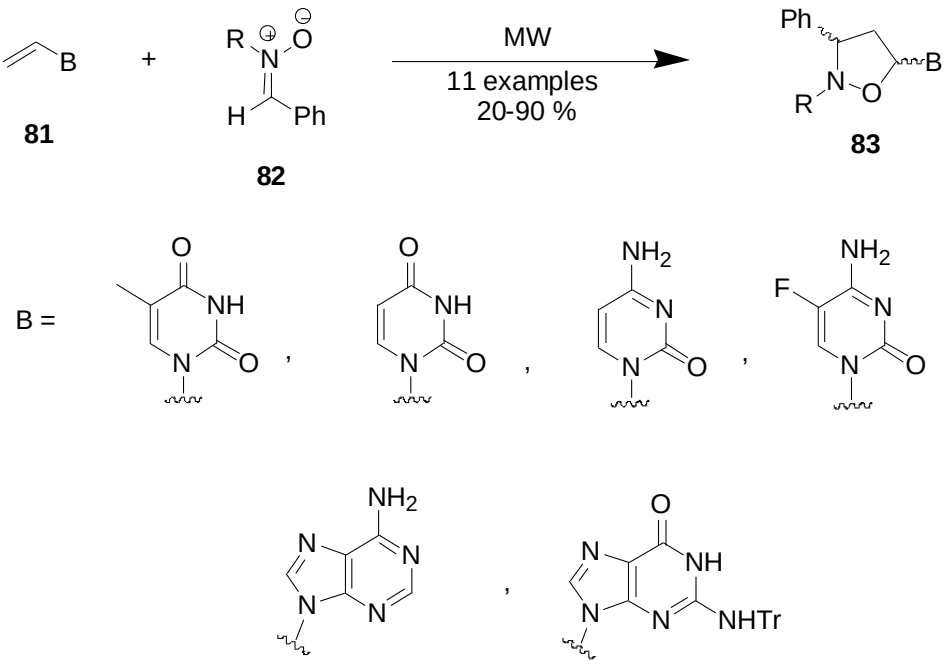
78

79a: 5R = 47%
79b: 5S = 48%

80

Scheme 26. Synthesis of isoxazolidinylthymines **80**.

More recently, Bortolini *et al*. have reported a more environmentally acceptable approach to the synthesis of a variety of non-easily-available 4'-aza-2',3'-dideoxy nucleosides **83**. Using a direct 1,3-dipolar cycloaddition between nitrones **82** and vinyl nucleobases **81**, the reaction was assisted by microwave irradiation, in the absence of solvent.[66] The cycloaddition reaction proceeded smoothly and it was possible to synthesize nucleosides **83** in good yields and short reaction times (10-50 mins). It was also possible to use the vinyl nucleobases in the reaction in their unprotected form.



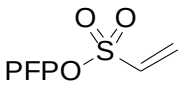
Scheme 27. Synthesis of 4'-aza-2',3'-dideoxy nucleosides **83**.

In conclusion, these examples illustrate the utility of nitrones in current organic synthesis, thus demonstrating that 1,3-dipolar cycloaddition is an important methodology for the construction of interesting biologically active molecules.

1.5 Chemistry of pentafluorophenyl/trichlorophenyl vinyl sulfonate

As discussed earlier, the sulfonamide unit is very important in medicinal chemistry. Because of this vast potential and the relative challenges associated with their preparation, new strategies to functionalized sulfonamides are continually being sought. This has led to the discovery and introduction of pentafluorophenyl sulfonate ester as a stable alternative to sulfonyl chlorides by Caddick *et al.*[67] Much of the work of Caddick has focused on the chemistry of sulfonate ester **85** – a bifunctional acceptor, which was easily prepared from commercially available pentafluorophenol and 2-chloroethane-1-sulfonyl chloride[68] that would be susceptible to attack from both radical and nucleophilic species. In addition, owing to the electron withdrawing nature of the PFP group, the sulfur centre would be susceptible to nucleophilic attack especially by amines, to make sulfonamides. To date, it has been found that the PFP sulfonate ester group is stable to a variety of

conditions including column chromatography, acidic and basic workup procedures and aqueous conditions.

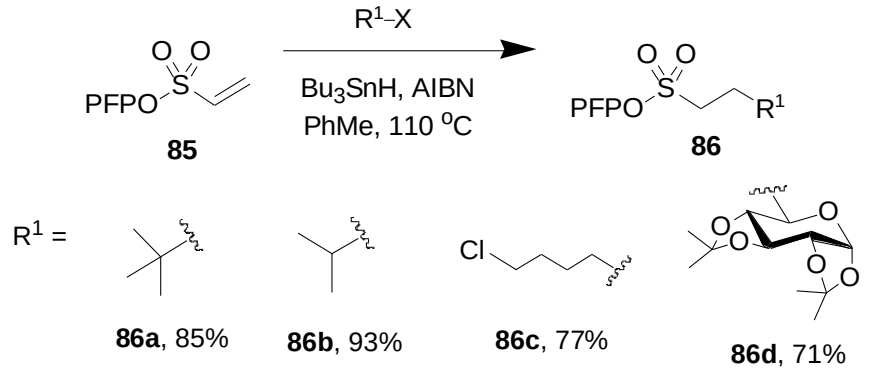


85

Figure 7. Structure of pentafluorophenyl vinyl sulfonate **85**.

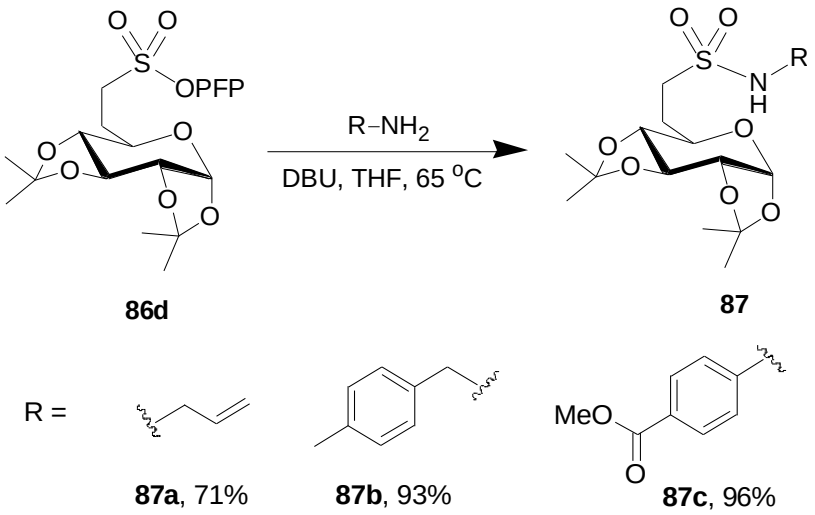
1.5.1 Radical chemistry

Caddick *et al*. have reported intermolecular tin-mediated radical addition of alkyl halides to PFP vinyl sulfonate mediated by tributyl hydride.[67] Reactions of **85** with alkyl radicals gave alkyl sulfonates **86** in good to excellent yields (Scheme 28). Caddick *et al.* also found that the reaction was not limited to simple alkyl or stabilized radical species but could be used in the synthesis of a derivatized sugar (for example **86d**) or amino species.



Scheme 28. Intermolecular radical addition with PFP vinyl sulfonate.

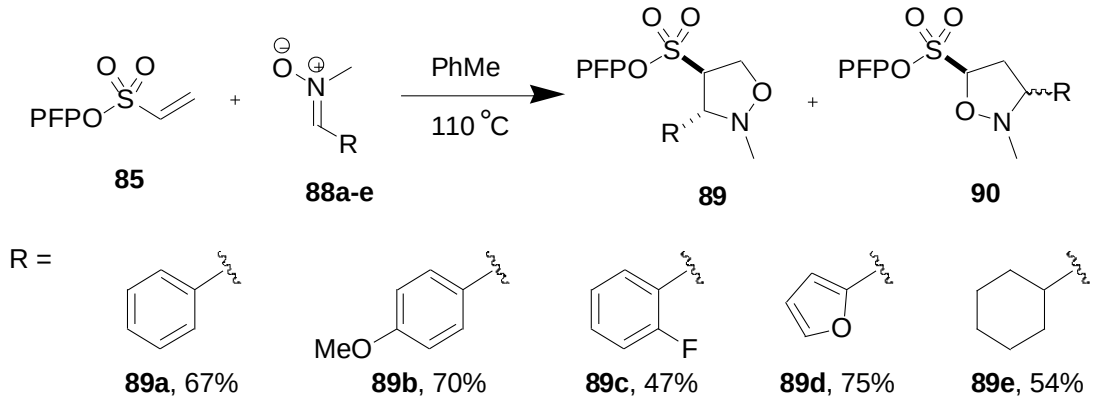
The alkyl sulfonate ester **86d** was treated with amines to displace the pentafluorophenol group which furnished the sulfonamides **87** in a good yield (Scheme 29).



Scheme 29. Aminolysis of sulfonate ester **86d**.

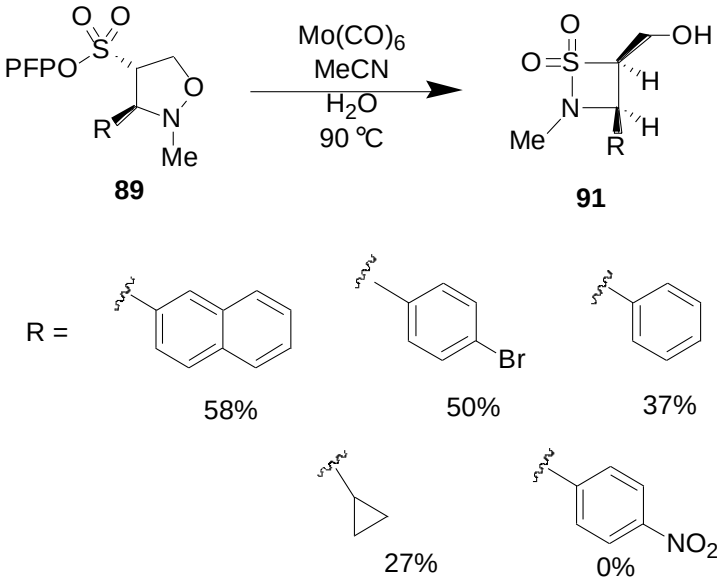
It was found that the aminolysis reaction proceeded when a strong base such as DBU or sodium hydride was present in the reaction medium. Because of this observation, they postulated that the reaction mechanism went *via* the deprotonation to the sulfonate moiety, followed by rapid extrusion of pentafluorophenol.[67]

Caddick *et al*. have also reported regioselective and diastereoselective 1,3-dipolar cycloaddition of PFP vinyl sulfonate ester **85** with a range of *N*-methyl nitrones to generate the a range of isoxazolidines **89**.[68] Cycloadditions to give isoxazolidines **89** were readily achieved upon reaction of vinyl sulfonate **85** with 1-2.5 eq. of nitrones **88** in toluene at 110 °C (Scheme 30). Cycloadditions were successful with a variety of C-aryl, **89a-c**, C-heteroaryl, **89d**, and C-alkyl nitrones, **89e**, with the highest yields obtained with electron rich nitrones, for example **89b** and **89d**. In all cases, with the exception of **89a**, cycloaddition of nitrones **88** with vinyl sulfonates **89** afforded only the corresponding C-4 trans isoxazolidines **89** with no evidence for the C-5 substituted isomers **90**.



Scheme 30. 1,3-dipolar cycloaddition reaction with PFP vinyl sulfonate **85**.

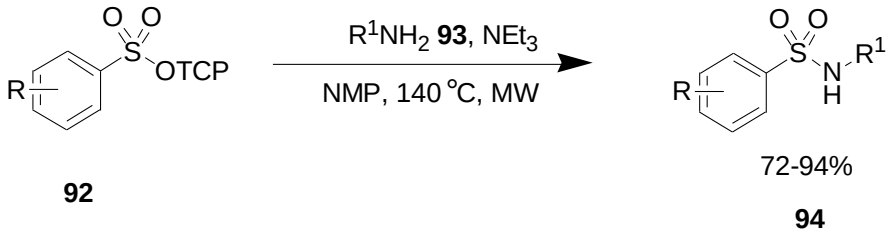
Caddick *et al.* have exemplified the utility of the isoxazolidine sulfonate **89** in the synthesis of β-sultams **91**, sulfur analogues of β-lactams, *via* selective ring cleavage of the N-O bond.[69] Reduction of the isoxazolidine N-O bond of **89** with $Mo(CO)_6$ afforded intermediate amine sulfonates which upon cyclisation gave β-sultams **91** in moderate yields (Scheme 31).



Scheme 31. Synthesis of β-sultams **91**.

Despite the synthetic advantages of the PFP esters, there has been a degree of resistance to their use on anything other than a small scale due to cost and perceived toxicity. This led to the introduction of 2,4,6-trichlorophenol (TCP) sulfonate[70] **92** as an ideal replacement due to its known lower toxicity and its low cost. TCP sulfonate **92** was synthesised from its corresponding sulfonic acid salt and triphenylphosphine ditriflate (see Scheme 1.1.6.2). The reactivity of TCP sulfonate **92** with amines was

then investigated (Scheme 32).[71] The aminolysis reaction of sulfonates **92** with amines **93** was readily achieved generating sulfonamide **94** in good to excellent yield. The reaction was tolerant to both simple nucleophilic amines and more challenging examples, such as anilines and hindered amines.



92 **94**

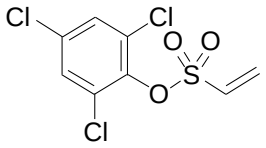
Scheme 32. Aminolysis of TCP sulfonates **92**.

In conclusion, Caddick *et al*. have shown from their comprehensive work that PFP (and more recently TCP) sulfonate esters, whether alkyl or aryl, are excellent alternatives to sulfonyl chlorides as many reactions can be carried out with the sulfonate present and thus provide a new route towards the synthesis of highly desirable sulfonamides.

Chapter 2 R&D: Studies on the intermolecular radical addition reactions of TCP vinyl sulfonate

2.1 Aim

The aim of this work was to explore the scope of intermolecular radical reactions of trichlorophenyl (TCP) vinyl sulfonate **95** (Figure 8). It had previously been found that pentafluorophenyl vinyl sulfonate can undergo radical addition mediated by tributyltin hydride (Section 1.4), and the present investigation is an extension of this work to trichlorophenyl vinyl sulfonates particularly their reactions with alkyl and acyl radicals.



95

Figure 8. Structure of TCP vinyl sulfonate **95**.

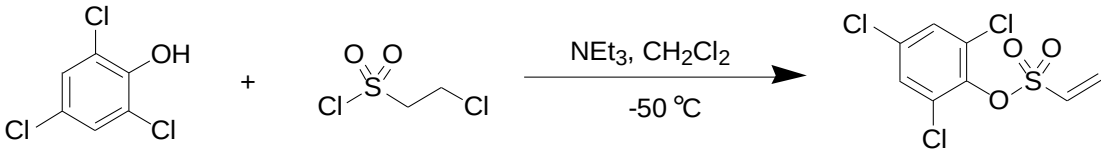
2.2 Intermolecular radical addition using alkyl radicals

Intermolecular radical reactions provide an attractive means of carbon–carbon bond formation due to their mild conditions and functional group tolerance. The most common and reliable way of generating alkyl radical involves reaction of halide or related precursor with tributyltin hydride and this had proven to be successful with PFP-vinyl sulfonate precursor. However, it was of interest to explore the use of tin-free radical reaction chemistry for this type of transformation. The use of phosphorous-centred radicals was an area of interest because of the relatively low cost. Low toxicity and commercial availability of 1-ethylpiperidinium hypophosphite (EPHP) **57**, led it to be chosen as a suitable radical chain carrier.

2.2.1 Synthesis of trichlorophenyl (TCP) vinyl sulfonate

Trichlorophenol (TCP) vinyl sulfonate was synthesized by the treatment of commercially available 2-chloroethane 1-sulfonyl chloride **97** with a suspension of trichlorophenol **96** and triethylamine (Scheme 33). This reaction is temperature sensitive as the starting materials decompose rapidly above 0 °C. As the addition of

the suspension of trichlorophenol and triethylamine is exothermic, it was added dropwise ensuring that the temperature remained below 0 °C. It was however found that maintaining the internal temperature at –50 °C and reduction of the equivalents of amine used from 3 to 2.3 lowered the amount of decomposition and the yield of the vinyl sulfonate **95** increased to 90% (Table 1, entry 3).



96 **97** **95**

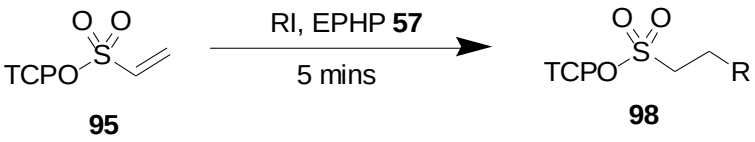
Scheme 33. Synthesis of TCP vinyl sulfonate **95**.

Table 1. Optimisation results for the synthesis of TCP vinyl sulfonate **95**.

Entry No	**NEt_3 (eq)**	**Temperature (°C)**	**Yield (%)**
1	3	0	44
2	3	–50	66
3	2.3	–50	90

2.2.2 Alkyl radical addition to TCP vinyl sulfonate

With TCP vinyl sulfonate **95** synthesised, radical additions were carried out. These reactions were mediated by EPHP **57**, as Caddick *et al.* had been successful mediating reactions with PFP acrylate with this chain carrier.[72] Their work also showed that alkyl bromides gave poor yields in these reactions and alkyl iodides were better substrates. Using their protocol (10 eq of EPHP, Et_3B/O_2, CH_2Cl_2) as a bench mark, a set of small scale reaction was carried out to find the optimum reaction conditions for vinyl sulfonate **95** to generate alkyl sulfonate **98**.



95 **98**

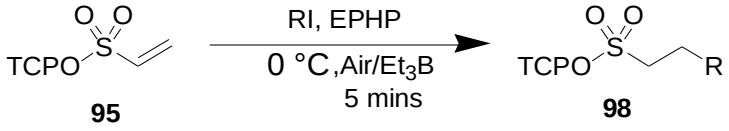
Scheme 34. Optimisation reaction of radical addition to TCP vinyl sulfonate **95**.

Table 2. Optimisation reaction results for Scheme 34.

Entry No	RI	EPHP 57 (eq)	Solvent	Initiator	Temp. (°C)	Yield (%)
1	i-Pr-I	5	1,4-dioxane	Air	RT	<5
2	i-Pr-I	5	1,4-dioxane	Air/Et_3B	RT	47
3	i-Pr-I	5	CH_2Cl_2	Air/Et_3B	RT	43
4	i-Pr-I	5	1,4-dioxane	Air/Et_3B	0	58
5	i-Pr-I	5	CH_2Cl_2	Air/Et_3B	0	62
6	t-Bu-I	5	CH_2Cl_2	Air/Et_3B	0	59
7	t-Bu-I	3	CH_2Cl_2	Air/Et_3B	0	50
8	t-Bu-I	7.5	CH_2Cl_2	Air/Et_3B	0	64
9	t-Bu-I	10	CH_2Cl_2	Air/Et_3B	0	63

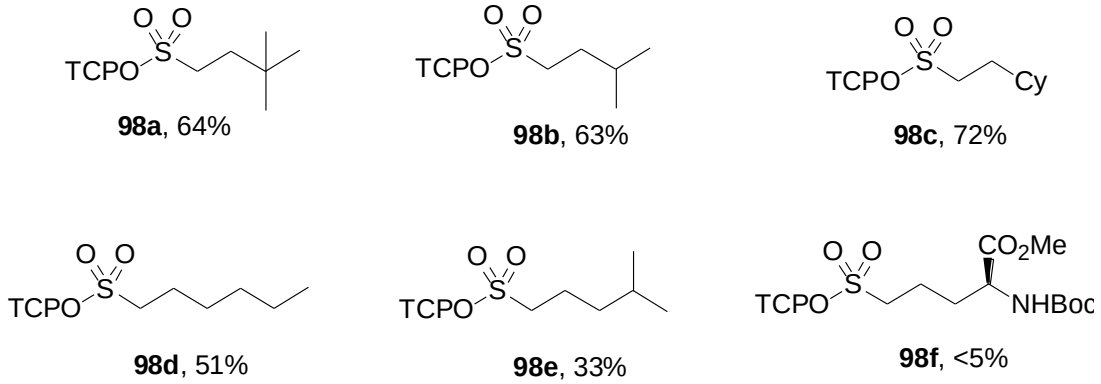
Optimisation of the reaction conditions for the radical addition of secondary and tertiary radicals to TCP vinyl sulfonate indicated that higher concentrations of chain carrier gave higher yields although the maximum yield was achieved at 7.5 eq of EPHP **57** (Table 2, entry 8) and increasing the concentration any further did not improve the yield. In addition, air alone did not initiate the free radical chain effectively (Table 2, entry 1) however the reaction with triethylborane/air mixture at low temperature was found to proceed smoothly. This was best achieved by passing a volume of air through the reaction solution under a static inert atmosphere. The temperature of the reaction was also critical as there was an improvement in the yield

on lowering the temperature of the reaction (Table 2, entries 3 and 5). The reactions were also particularly facile requiring a reaction time of just 5 mins and the major side products, hypophosphite derived, could be removed with an aqueous work-up. Having established the optimum conditions (7.5 eq, Et_3B/air, 0 °C, CH_2Cl_2) to addition to vinyl sulfonate **95**, a variety of alkyl iodides incorporating different functional groups were used (Figure 9).



95 **98**

Scheme 35. Intermolecular radical addition to TCP vinyl sulfonate **95** using EPHP.



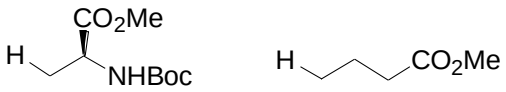
98a, 64% **98b**, 63% **98c**, 72%

98d, 51% **98e**, 33% **98f**, <5%

98g, 27% **98h**, <5%

Figure 9. Results of Scheme 35.

The yields of the alkyl sulfonate **98** were generally moderate to good, although lower yields were observed with the primary alkyl halides. The low yield could be attributed to significant amounts of iodide reduction products which were observed in the crude NMR spectrum. Together with the iodide reduction, one of the other possible side reactions that can become more dominant is the addition of the ethyl radical generated from triethylborane to vinyl sulfonate **95**. This ethyl radical is very reactive and would add much more readily and this effect is seen quite dramatically in the yields low of products **98f** and **98h**. Here significant amounts of the iodide reduction and ethyl radical addition were obtained even at low temperatures giving products **99** and **100** respectively (Figure 10).

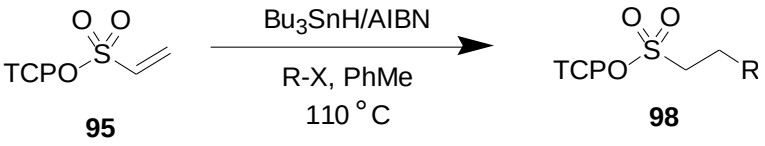


99, 61% **100**, 21%

Figure 10: Isolated side products

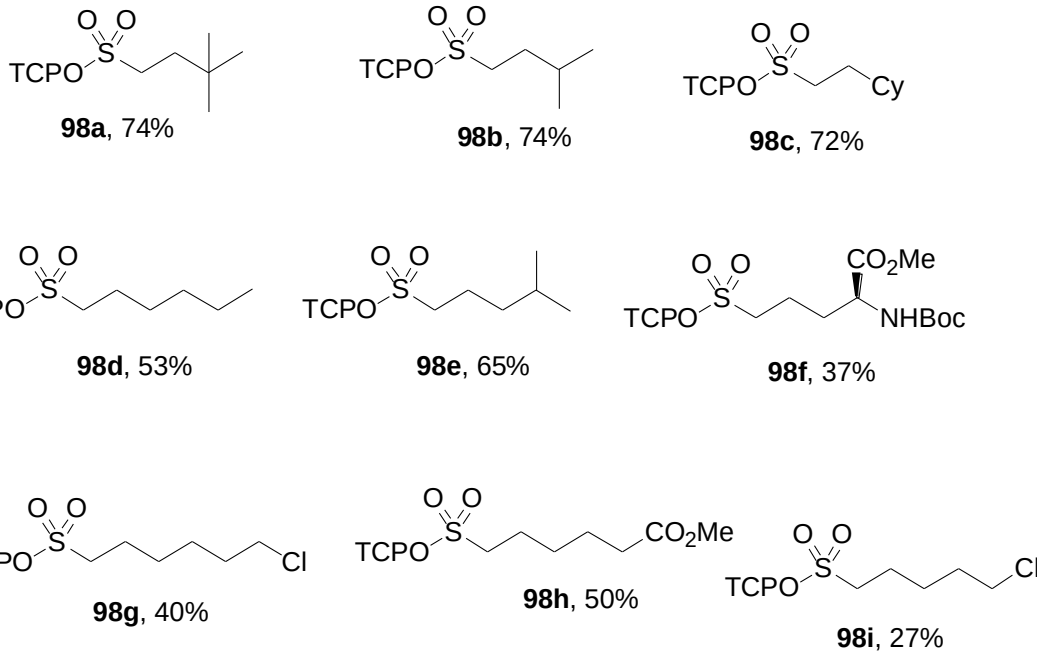
2.2.3 Intermolecular radical addition using tributyltin hydride

Although the use of EPHP as a chain carrier was successful, problems with the efficiency of the reaction particularly with primary iodides as mentioned above limited the scope of the methodology. In order to expand the generality of the reaction, Bu_3SnH was used as the radical chain carrier using the procedure from Caddick *et al.*[72]



95 **98**

Scheme 36. Intermolecular radical addition to TCP vinyl sulfonate **95** using Bu_3SnH.



98a, 74% **98b**, 74% **98c**, 72%

98d, 53% **98e**, 65% **98f**, 37%

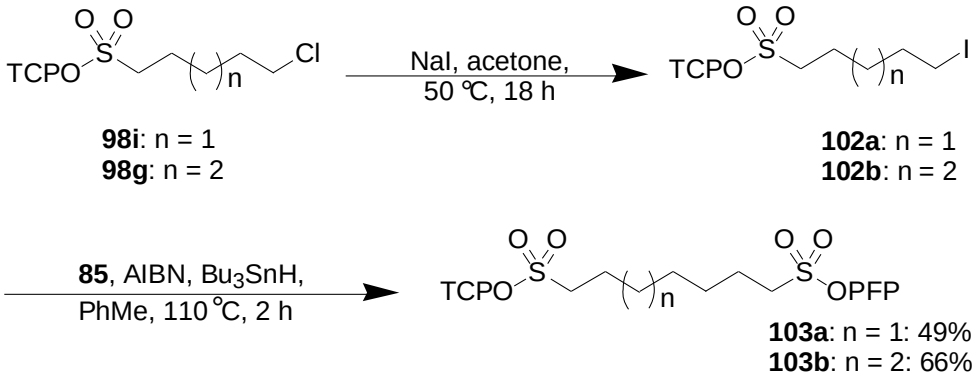
98g, 40% **98h**, 50% **98i**, 27%

Figure 11. Results from Scheme 95.

Using the chain carrier, $Bu_3Sn^{\bullet}$, formed by reaction with AIBN in refluxing toluene produced the corresponding alkyl sulfonate esters in moderate to good yields. The tin residue was removed by stirring the reaction mixture with potassium fluoride for 18 hours and then filtering the insoluble tin fluoride through Celite®. The effectiveness

of this intermolecular radical addition is exemplified in the addition of the primary halides particularly in producing **98f** and **98h**, which were previously unsuccessful with EPHP **57** as the chain carrier but was successful in the presence of Bu_3SnH. However, as before significant amounts of halide reduction and HI elimination products were isolated.

Encouraged by these results, the scope of this reaction was expanded further by preparing a bifunctional alkyl TCP/ PFP sulfonate *via* a double radical addition protocol (Scheme 37). It was envisaged that the product of this double addition could be used to explore the reactivity of PFP and TCP in a two-directional synthesis.



Scheme 37. Double intermolecular radical addition

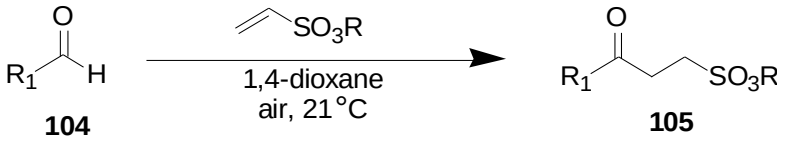
An initial trial of the halide exchange at room temperature over 24 hours gave a mixture of the iodo-product **102** and the unreacted chloro-starting material **101**. Increasing the temperature to 50 °C improved the conversion ratio and the iodide **102** thus obtained was used in the following step without purification. Radical addition to PFP vinyl sulfonate using iodides **102a** and **102b** gave the desired bifunctional TCP/PFP sulfonates **103a** and **103b** in moderate yields.

2.3 Intermolecular acyl radical addition to vinyl sulfonates

The generation of acyl radicals and their reactions with alkenes has long been recognised as a useful and practical method of generating carbon-carbon bonds.[73,74] Acyl radicals were first reported by Kharasch *et al.*[75] in 1949 where the peroxide-initiated free radical of aldehydes were added to simple olefins. The method was then extended to the more productive use of electron-deficient alkenes.[76] Since then additional free radical chain initiation methods have been introduced, and examples

of intramolecular and intermolecular acyl radical-alkene addition reactions have been described.[74]

One of such examples includes the hydroacylation reaction reported by Caddick *et al*. In their report, keto-sulfonates **105** were generated by mixing the vinyl sulfonates **85** or **95** with aldehydes **104** in ethereal solvents such as dioxane and ethylene glycol dimethyl ether, at room temperature.[77] The authors found that the transformation proceeds with a variety of aliphatic aldehydes. They found however that the isolated yields for reactions with the PFP-derived olefin **85** are generally lower than those with the corresponding TCP-derivative although the reactions were universally faster with the PFP substrate. The lower yields were attributed to the reduced stability of PFP groups to purification by flash chromatography on silica gel.



104 **105**

Scheme 38. Synthesis of keto-sulfonate **105**.

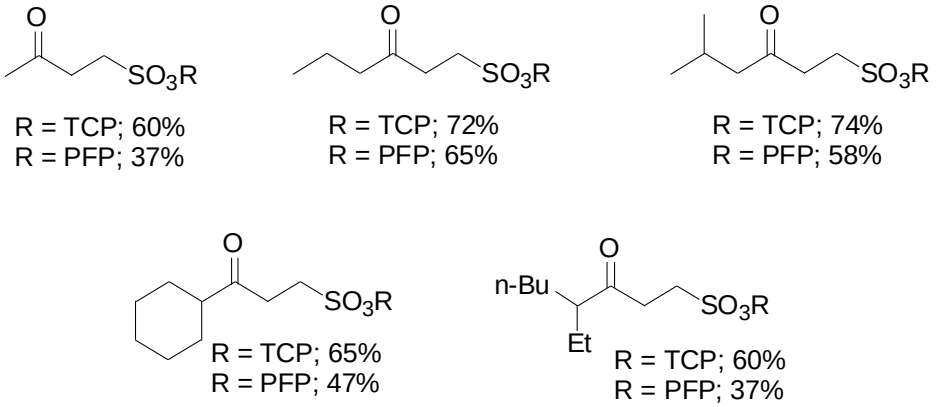
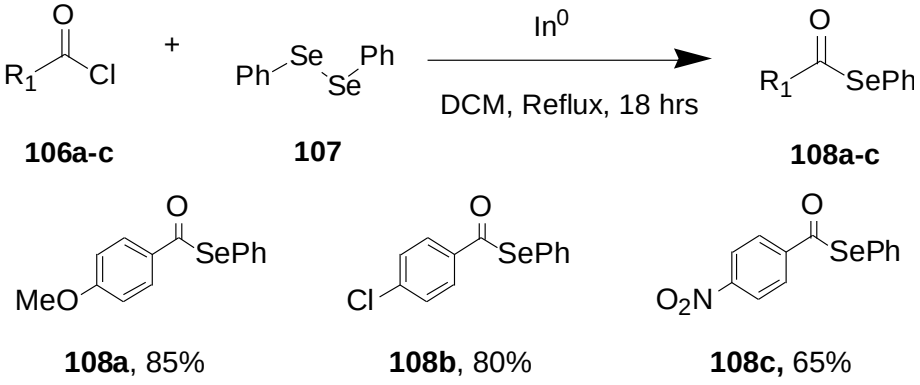


Figure 12. Results from Scheme 38.

The authors also attempted the hydroacylation reaction with aromatic aldehydes but they were unsuccessful.[78] Other ways of generating acyl radicals were then investigated. Of the three possible ways of generating acyl radicals,[79] generation from homolytic rupture of a RC(O)-X is still the most widely applied particularly in the generation of these radicals by reaction of the corresponding selenoesters with tin hydride.

2.3.1 Synthesis of selenoesters

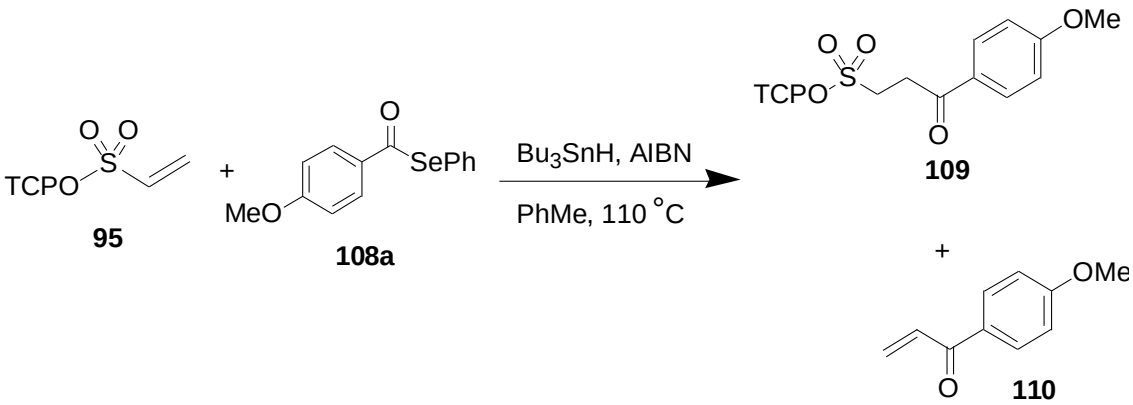
To synthesise the selenoester required, the procedure reported by Braga *et al.*[80] employing indium was used. This procedure utilised mild conditions (reflux in CH_2Cl_2 for 18 hours) and the selenoester **108** was synthesised in an excellent yield (Scheme 39).



Scheme 39. Synthesis of selenoester **108**.

2.3.2 Acyl radical addition to TCP vinyl sulfonate

With the selenoesters **108a-c** in hand, the reaction with vinyl sulfonate **95** and selenoester **108a** was investigated using tributyltin hydride initiated by AIBN as used in synthesis by Boger *et al.* (Scheme 40).[74]

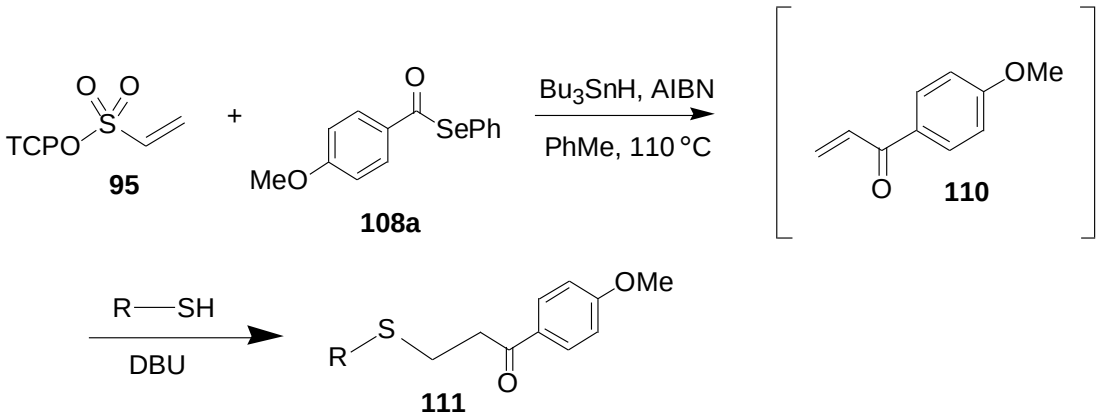


Scheme 40. Acyl radical addition to TCP vinyl sulfonate **95**.

Selenoester **108a** was added to vinyl sulfonate **95** and heated to reflux for 2 hours. TLC analysis of the reaction indicated formation of a new product spot during the reaction, and analysis of NMR spectrum of the crude reaction mixture showed formation of expected product **109** along with unreacted starting materials **95** and **108a**. However, analysis of NMR spectrum of the isolated product after column

chromatography did not correspond to the expected product **109**. Instead, some of the NMR peaks corresponded to enone **110**. Several attempts using the same conditions gave similar results. Presumably the formation of enone **110** is encouraged by both the elevated reaction temperature (110 °C) and the purification on silica gel.

Although some of the enone **110** was isolated, it was quite unstable and rapidly decomposed so it was not fully characterised. To confirm that the enone **110** was been formed a trapping reaction was carried out using a thiol. It was envisaged that upon formation of enone **110**, the thiol would add in a Michael addition to generate the thiol **111**. The radical addition reaction using selenoester **108a** was carried out with vinyl sulfonate **95** mediated with tributyltin hydride and heated to reflux for 2 hours (Scheme 41). DBU and thiol were added to the reaction mixture after two hours and the reaction monitored by TLC. TLC analysis showed formation of a new spot after 30 minutes.



Scheme 41. Trapping reaction using a thiol.

Despite several attempts at this reaction using same conditions, efforts towards isolating any product **111** proved futile.

2.4 Summary

This study has established TCP vinyl sulfonate has a good substrate for free radical addition reactions. The alkyl radical addition reactions were successfully carried out using tin-free protocol, using EPHP **57** initiated by Et_3B/air and tin protocol, Bu_3SnH initiated by AIBN to generate alkyl radicals. Although the EPHP **57** protocol was successful, it was greatly limited by its efficiency particularly with primary alkyl radicals. Notably, the success of the double intermolecular radical addition to prepare bifunctional TCP/PFP sulfonates could be applied in our continued investigation in the reactivity of the vinyl sulfonates.

The acyl radical addition reaction was not as successful as its alkyl counterpart in generating the corresponding acyl sulfonates. We suggest this was due to the formation of an enol after the addition and subsequent elimination to generate the enone. An attempt at trapping the reactive enone with thiols proved unsuccessful.

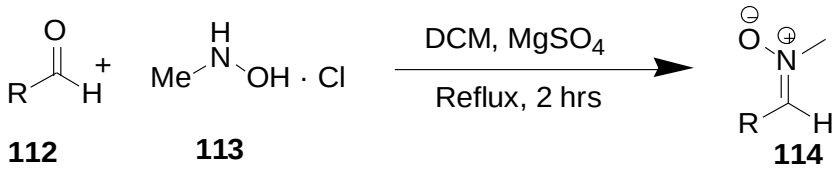
Chapter 3 R&D: Studies on the 1,3-dipolar cycloaddition reactions of PFP/TCP vinyl sulfonate

3.1 Aim

Previous work within the group has shown PFP vinyl sulfonate to be a good dipolarophile.[68,72] The aim of this project is to continue this research and explore the reactivity of the vinyl sulfonates in 1,3-dipolar cycloaddition particularly with TCP vinyl sulfonate.

3.2 Synthesis of Nitrones

Nitrones are readily available compounds that can be obtained from aldehydes, amines, imines and oximes, and are well known to behave as 1,3-dipoles in cycloaddition reactions to form a variety of stable five membered heterocyclic ring systems.[56,57] Nitrones (or azomethine oxides) are one of the most widely studied dipoles[57] and were prepared in excellent yield *via* the condensation of aldehyde **112** with an *N*-substituted hydroxylamine **113** (Scheme 42).[68]



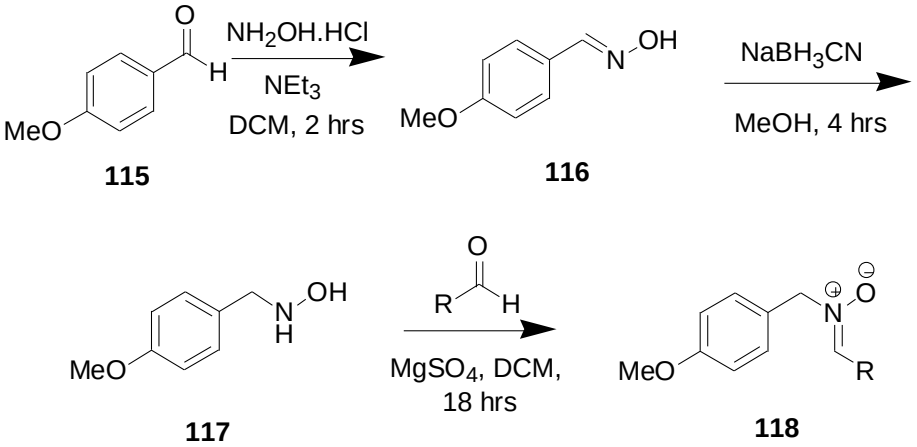
112 **113** **114**

Scheme 42. Synthesis of *N*-methyl nitrone **114**.

Table 3. Results obtained from Scheme 42.

Product No	R-group	Yield (%)
114a	Ph	70
114b	*p*-MeO.C_6H_4	67
114c	*p*-NO_2 C_6H_4	50
114d	$C_{10}H_7$	80
114e	Furyl	65
114f	Cyclopropyl	80

In addition to using *N*-methyl nitrone **114**, our studies also utilised *N*-PMB nitrone **118** (see Scheme 43), whereby the PMB protecting group can be removed to allow for further manipulations of the product. The PMB-hydroxylamine **117** was synthesised by reacting anisaldehyde **115** with hydroxylamine.HCl and then reducing the resulting oxime **116** with $NaBH_3CN$.[81] With hydroxylamine **117** in hand, *N*-PMB nitrones **118a-e** were synthesised using a variety of aldehydes incorporating electron-withdrawing and electron-donating properties. The reaction proceeded very smoothly usually not requiring purification although recrystallising the crude product gave easy to handle material.



Scheme 43. Synthesis of *N*-PMB nitrone **118**.

Table 4. Results from obtained Scheme 43.

Product No	R-group	Yield (%)
118a	*p*-MeO.C_6H_4	75
118b	*o*-Cl. C_7H_4	65
118c	Ph	72
118d	Cyclohexyl	60
118e	$C_{10}H_7$	92

3.3 1,3-Dipolar cycloaddition of vinyl sulfonate with nitrone

The success of the cycloaddition of PFP vinyl sulfonate **85** with *N*-Me nitrones to yield regio- and diastereo- selective isoxazolines,[68] encouraged the extension of the chemistry to TCP vinyl sulfonate as this would give a more cost effective and less toxic route to the isoxazoline intermediates. We were particularly interested in the reactivity of *N*-PMB nitrones in the cycloaddition reaction. Using *N*-PMB nitrone **118a**, optimisation reaction was carried out using vinyl sulfonate **85** (Scheme 44).

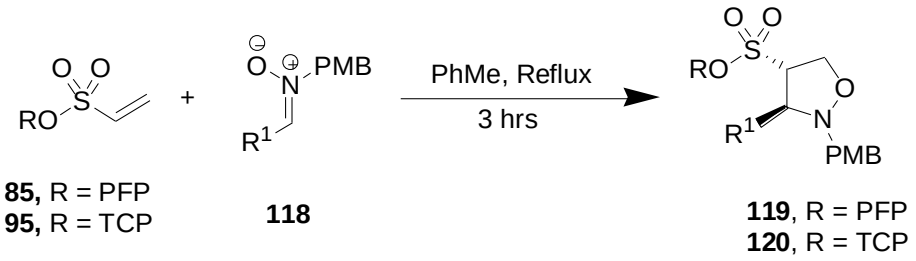
85 **118a** **119a**

Scheme 44. Optimisation of cycloaddition to PFP vinyl sulfonate **85**.

Table 5. Optimisation reaction results of Scheme 44.

Entry No	Nitrone (eq)	Time (hrs)	Temp (°C)	Yield (%)
1	2	18	23	38
2	2	3	23	58
3	1	3	110	64

Cycloaddition with 2 equivalents of nitrone **118a** at 23 °C for 18 hours gave isoxazolidine **119a** in a poor yield of 38%. This yield was improved to 58% by shortening the reaction time to 3 hours. However, the highest yield was obtained when the reaction was carried out using 1 equivalent of nitrone **118a** at reflux for 3 hours (Table 5, entry 3). Using the optimal conditions (reflux for 3 hours using 1 equivalent of nitrone) a small collection of *N*-PMB isoxazolidines were synthesised.



Scheme 45. Synthesis of *N*-PMB isoxazolidines **119** and **120**.

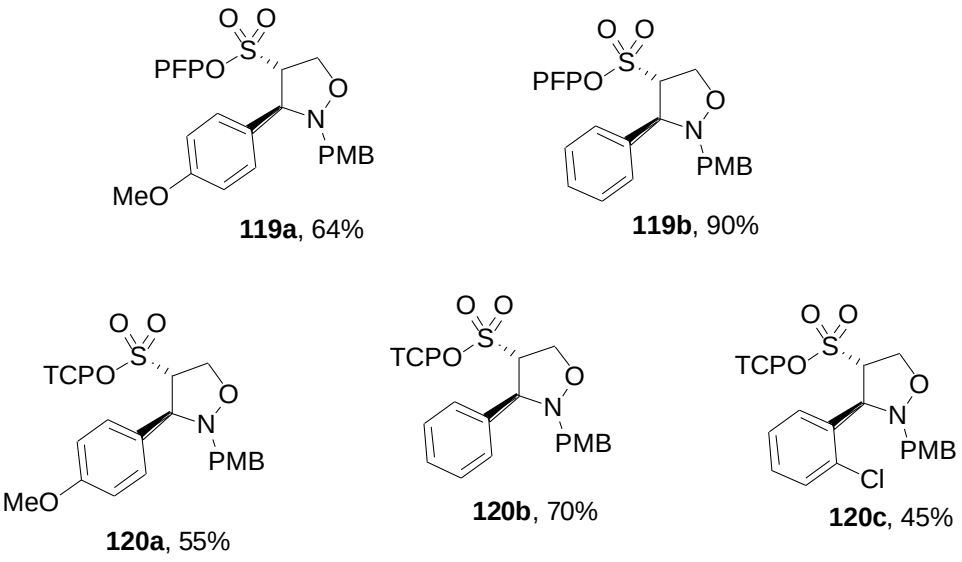


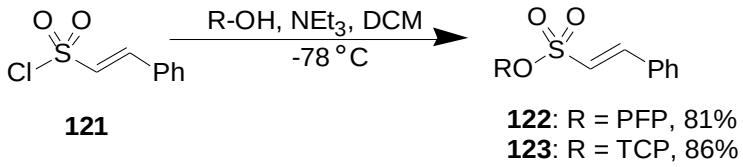
Figure 13. Results from Scheme 45.

The reaction with TCP vinyl sulfonate **95** was slower and gave a lower yield than PFP vinyl sulfonate **85** (Figure 14, **119b** and **120b**). The electronics of the R-group on the nitrone seemed to have an effect on the yield of the reaction. With electron donating groups (Figure 14, **119a** and **120a**), the yield obtained was moderate, but a much lower yield was obtained with the electron withdrawing group (Figure 14, **120c**).

The yields obtained using the *N*-PMB nitrone compared favourably with those obtained previously within the group using the simple *N*-Me nitrones.[81] Comparing the NMR spectra obtained with the NMR spectra of isoxazolidines previously synthesised by Mok[81] confirmed that the products obtained from the reactions with the *N*-PMB nitrones were in all cases the *trans* 4C-isoxazolidines.

3.3.1 Cycloaddition with β-phenyl PFP vinyl sulfonate

Cycloaddition with β-phenyl vinyl sulfonate was next investigated as a means of exploring the reactivity scope of the vinyl sulfonates. Formation of β-phenyl vinylsulfonates **122** and **123** was achieved by reacting commercially available sulfonyl chloride **121** with the corresponding alcohol at –78 °C (Scheme 46).

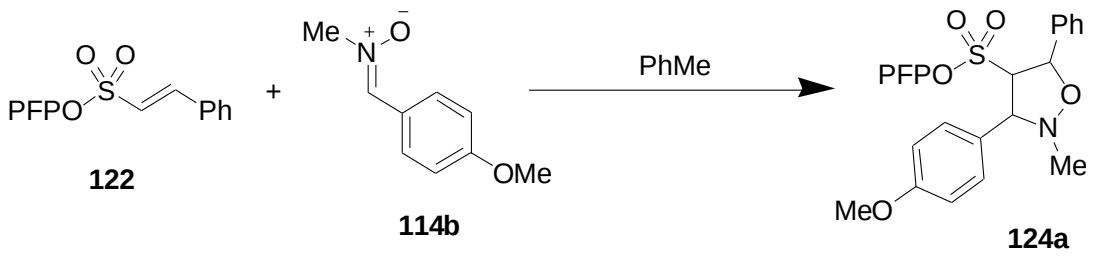


121

122: R = PFP, 81%
123: R = TCP, 86%

Scheme 46. Synthesis of β-phenyl vinyl sulfonates **122** and **123**.

Having the phenyl group in the β position changes the sterics and the electronics of the vinyl sulfonate; however, it was envisaged that if the cycloaddition occurred, it would probably require elevated temperatures. An initial study towards reaction optimisation involved examination of the effect of temperature and nitrone concentration on the reaction of vinyl sulfonate **122** with nitrone **114b** in toluene (Scheme 48).



Scheme 47. Optimised reaction with β-Ph vinyl sulfonate **122**.

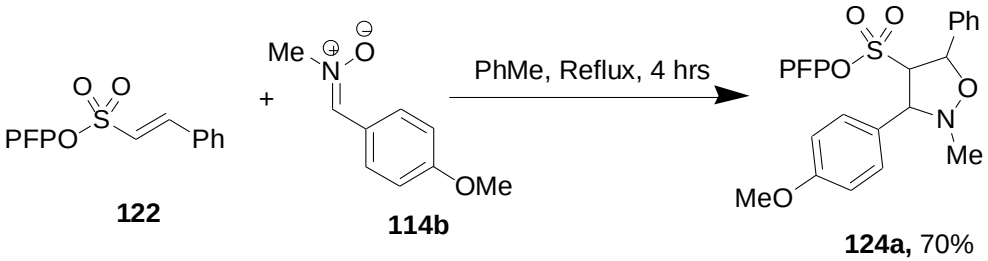
Table 6. Results of optimised reaction obtained from Scheme 47.

Entry	**Temp** (°C)	**Nitrone (**eq**)**	**Time (**hrs**)**	**Yield** (%)	**114 recovered** (%)
1	50	2	18	5	34
2	110	2	4	61	23
3	110	2	18	35	28
4	110	1.5	4	53	25
5	110	5	4	57	7*

* 20% aldehyde recovered

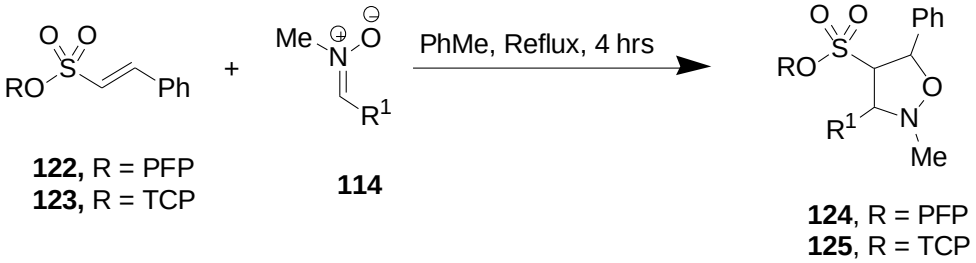
It was pleasing to observe cycloaddition to give isoxazolidine **124a** was readily achieved upon reaction of vinyl sulfonate **122** with nitrone **114a** in toluene. In all cases analysis of the NMR spectrum confirmed only the 4C isomer was formed. Also only one distereoisomer was obtained although the relative stereochemistry was unknown at this stage. From the results obtained, the highest yield (61%) was obtained at reflux in toluene for 4 hours using 2 eq of nitrone **114** although this was just at 77% conversion to **124a** as 23% vinyl sulfonate **122** was recovered.

As the conversion from the starting material was not 100%, we envisaged that the reaction could be forced to completion by addition of an extra equivalent of nitrone during the reaction. However, when this reaction was carried out with the addition of extra nitrone one hour into the reaction, there was an improvement on the yield from 61% to 70%, but the corresponding aldehyde, 20%, and the starting vinyl sulfonate **122**, 5%, were also isolated (Scheme 48).



Scheme 48. 1,3-Dipolar cycloaddition reaction of β-Ph vinyl sulfonate **122** using extra equivalent of nitrone

Following the success of cycloaddition with nitrone **114b** with PFP vinyl sulfonate **122**, other functionalized nitrones were employed in the cycloaddition reaction to investigate the scope of the reaction with both PFP and TCP vinyl sulfonates **122** and **123** respectively.

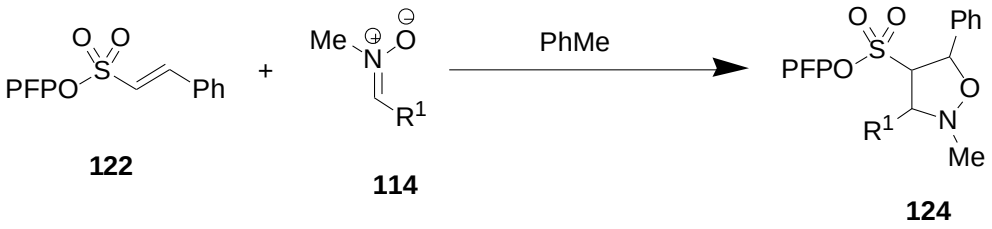


Scheme 49. 1,3-Dipolar cycloaddition reaction of β-Ph vinyl sulfonate **122** and **123**.

Table 7. Results obtained from Scheme 49.

Entry	Product No	R^1	Yield (%)	Recovered SM (%)
1	**124a**	*p*-MeO.C_6H_4	61	20
2	**124b**	Ph	61	18
3	**124c**	*p*-Br.C_6H_4	57	20
4	**124d**	Cyclopropane	0	25
5	**124e**	Cyclohexane	33	22
6	**124f**	*p*-NO_2 .C_6H_4	12	25
7	**124g**	$C_{10}H_7$	65	21
8	**125a**	*p*-MeO.C_6H_4	44	20
9	**125b**	Ph	60	20
10	**125c**	*p*-Br.C_6H_4	25	27

The yields obtained for this reaction varied between 0% and 61%; however, in all cases these were not a 100% conversion of vinyl sulfonate **122** and **123**. The variation in the yields obtained could be attributed to the stability of the nitrone (Table 7, entry 5 and 6) and its solubility (Table 7, entry 6). The yields of these reactions were improved by either reducing the temperature (Table 8, entry 1) or leaving the reaction for longer (Table 8, entry 2).



122 **114** **124**

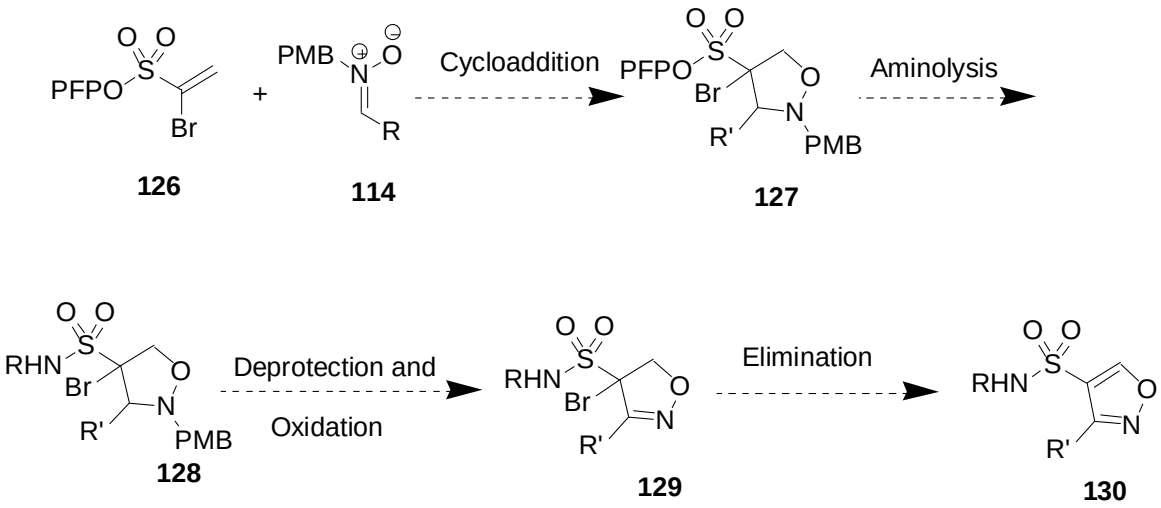
Scheme 50. 1,3-Dipolar cycloaddition reaction using β-Ph vinyl sulfonate **122**.

Table 8. Improved reaction results of Scheme 50.

Entry	R	Conditions	Yield (%)
1	cyclopropane	80 °C, 18 hrs	22
2	*p*-$NO_2.C_6H_4$	110 °C, 48 hrs	27

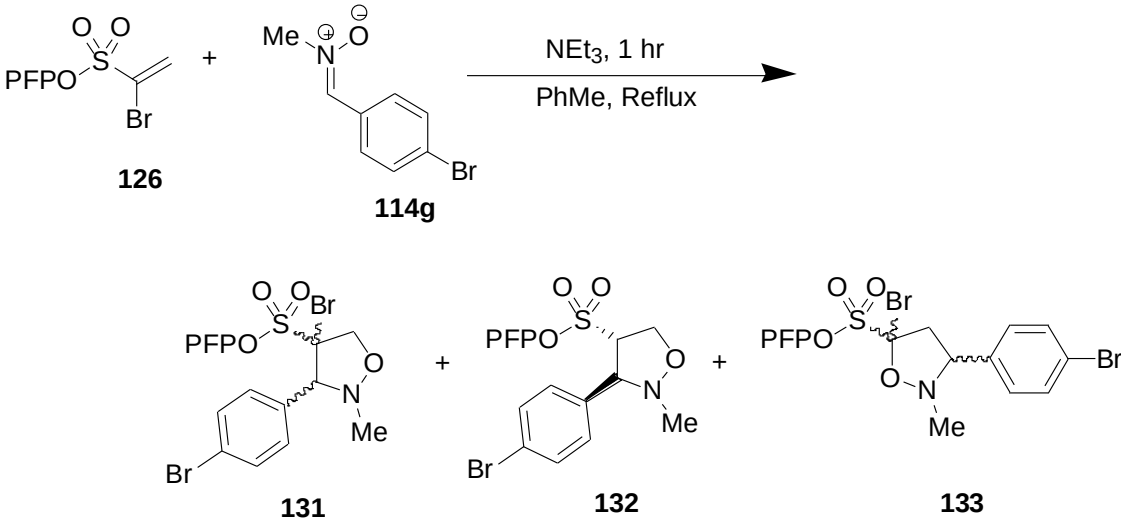
3.4 Cycloaddition studies with α-Br PFP/TCP vinyl sulfonates

The investigation continued with an examination of the potential of this reaction to be applied to the synthesis of the analogous isoxazole. After some model studies by Mok,[81] it was proposed that this reaction could be achieved by the use of α-bromo-PFP-vinyl sulfonate **126**, an established alkyne alternative within the group and a direct replacement for PFP vinyl sulfonate **85** in the cycloaddition reaction. Once the isoxazolidine **127** was formed, aminolysis could be carried out to form the sulfonamide **128**. It was then envisaged that deprotection of the PMB group followed by oxidation would yield compound **129** and subsequent elimination on HBr would yield isoxazole **130** (Scheme 51).



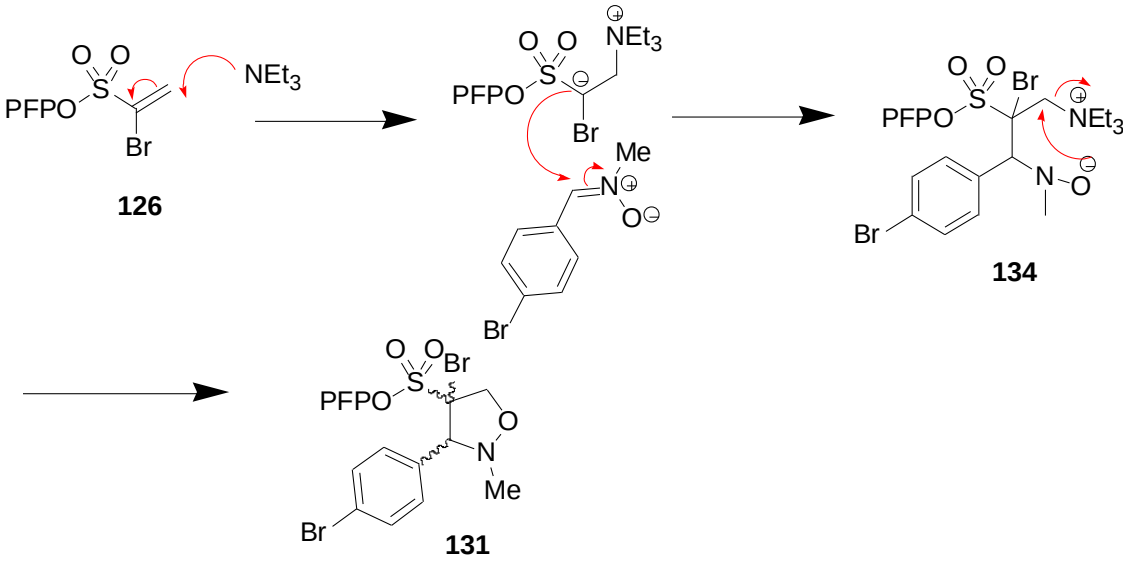
Scheme 51. Proposed reaction pathway for the synthesis of isoxazole **130**.

Previous work within the group showed that the use of *N*-Me nitrone **114g**[81] under the previously described conditions for cycloaddition (1.5 eq. nitrone and 1 eq. of dipolarophile in refluxing toluene) gave no product after 20 hours with only recovered starting material. However, upon addition of base, a mixture of products **131-133** were obtained (Scheme 52).[81]



Scheme 52. 1,3-Dipolar cycloaddition of α-Br vinyl sulfonate **126**.

It was postulated that the cycloaddition was in fact proceeding *via* a stepwise process bearing some similarity to the Baylis-Hillman reaction[82] and this would account for the formation of product **131** (Scheme 53).

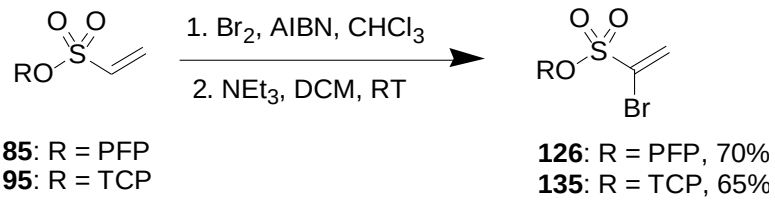


Scheme 53. Proposed reaction mechanism for the formation of isoxazolidine **131**.

Other tertiary bases were tested in this reaction and the analyses of the results showed that using 0.1 eq of DABCO at RT, it was possible to eliminate the de-brominated product **132**, reduce the amount of the 5C-product **133** and also increase the overall yield obtained.[81] The mechanism for this reaction remained unclear and therefore further studies were needed to explore the reactivity of the α-Br vinyl sulfonate **126** and its reaction scope.

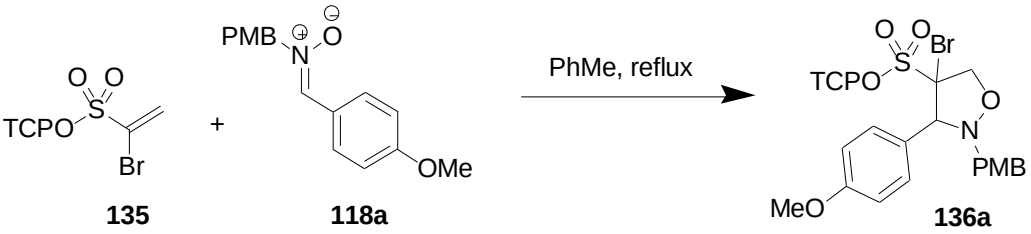
3.4.1 Cycloaddition reaction of α-Br PFP/TCP vinyl sulfonate – optimisation with a range of nitrones

The synthesis of brominated PFP vinyl sulfonate **126** and brominated TCP vinyl sulfonate **135** were achieved *via* a radical mediated process analogous to that described by Mok.[81] The brominated vinyl sulfonates was readily afforded in two stages. The first stage was the radical addition of bromine to vinyl sulfonate mediated by AIBN in chloroform followed by addition of NEt_3 to the residue from the first stage at RT leading to the elimination of HBr (Scheme 54).



Scheme 54. Synthesis of α-Br vinyl sulfonate **126** and **135**.

With sulfonates **126** and **135** synthesised, optimisation studies for the cycloaddition were carried out using brominated vinyl sulfonate **135** with *N*-PMB nitrone **118a** in toluene at reflux. Optimisation of the reaction showed that highest yield of isoxazolidine **136a** was obtained when brominated vinyl sulfonate **135** was reacted with *N*-PMB nitrone at 110 °C for two hours (Table 9, entry 3). At a longer reaction time (Table 9, entry 4) the reaction only resulted in decomposed material.



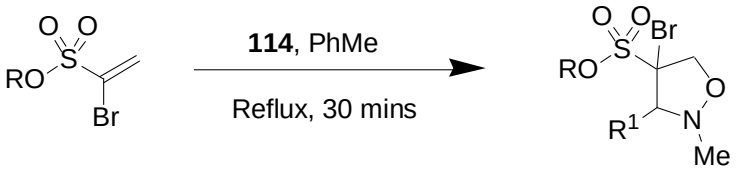
135 **118a** **136a**

Scheme 55

Table 9. Results obtained from Scheme 55.

Entry	**Time** (hrs)	**Temp.** (°C)	**Yield** (%)
1	6	90	64
2	18	90	60
3	2	110	75
4	18	110	decomposed

Using the optimal conditions (2 eq of nitrone at 110 °C for 2 hours), the cycloaddition reaction was carried out using other nitrones incorporating both electron-donating and electron-withdrawing groups.



126, R = PFP
135, R = TCP

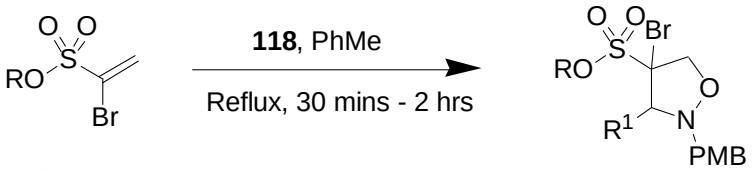
136, R = TCP
137, R = PFP

Scheme 56. 1,3-Dipolar cycloaddition reaction using *N*-Me nitrones **114**.

Table 10. Results obtained from Scheme 56.

Entry	**Product No**	**R^1**	**Yield (%)**
1	**136a**	Ph	78
2	**136b**	*p*-MeO.C_6H_4	70
3	**137a**	Ph	71
4	**137b**	*p*-MeO.C_6H_4	72
5	**137c**	*p*-Cl.C_6H_4	82
6	**137d**	*p*-Br.C_6H_4	76
7	**137e**	2-Br-furyl	45
8	**137f**	furyl	36
9	**137g**	*p*-NO_2.C_6H_4	46*

* diastereoisomers



126, R = PFP
135, R = TCP

138, R = TCP
139, R = PFP

Scheme 57. 1,3-Dipolar cycloaddition using N-PMB nitrones **118**.

Table 11. Results obtained from Scheme 57.

Entry	Product No	R^1	Yield (%)
1	**138a**	Ph	81*
2	**138b**	*p*-MeO.C_6H_4	71
3	**138c**	*p*-Br.C_6H_4	65
4	**138d**	$C_{10}H_7$	54*
5	**138e**	*p*-Cl.C_6H_4	52
6	**139a**	Ph	65*
7	**139b**	*p*-MeO.C_6H_4	86
8	**139c**	*p*-Br.C_6H_4	37

* diastereoisomers

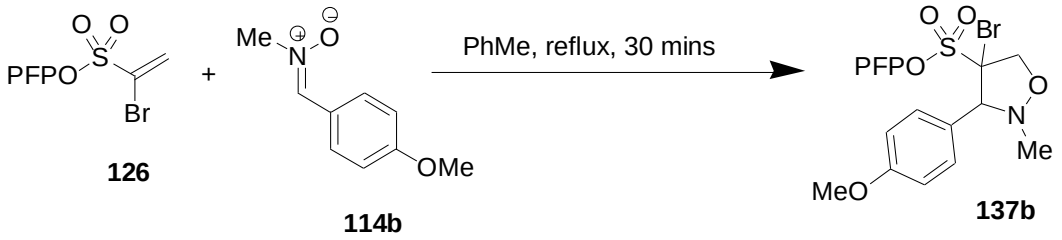
The cycloaddition reactions were successful in yielding the isoxazolidines in moderate to good yield. It was observed that the reactions with *N*-Me nitrones gave best yields at a reaction time of 30 minutes but the reaction times of the reactions with the *N*-PMB nitrones varied between 30 minutes and 2 hours. There was no obvious correlation between the yield and the nature of the nitrone and the alkene, as good yields were obtained both with electron-withdrawing and electron-donating groups (Table 10, product no **137b-d**), although poor yields were also obtained for electron-withdrawing group (Table 10, product no **137e-g**).

Analysis of the NMR spectra confirmed that the substituted isoxazolidines produced were all 4C isomers i.e. the reaction was regio-specific, although the reaction was not

distereo- selective as mixtures of diastereoisomers were formed in some reactions (Table 10 and 11, product no **137g**, **138a** and **139a**).

3.4.2 Catalysis of cycloaddition reaction of α-Br PFP/TCP vinyl sulfonate

As described earlier (section 3.4), previous work by Mok had shown the cycloaddition reaction with α-Br PFP vinyl sulfonate **126** and nitrone **114g** gave an improved yield on the addition of 0.1 eq of DABCO although the reaction was non-selective. From the results obtained in section 6.4.1, it was obvious that the cycloaddition reaction needed a shorter reaction time otherwise decomposition was observed. With this knowledge, the next stage was to investigate the 1,3-dipolar cycloaddition reaction of the brominated vinyl sulfonate with nitrone and its possible catalysis by bases. Using simple tertiary and secondary bases, the cycloaddition reaction was carried out with substrates **126** and **114b**. The cycloaddition reactions were all successful and gave good yields. However there was not any clear distinction between the yields of the isoxazolidine and the bases used, although the isolated product was still the 4C regioisomer. Subsequent investigations were carried out with DABCO as base due to its ease of handling as a crystalline solid.

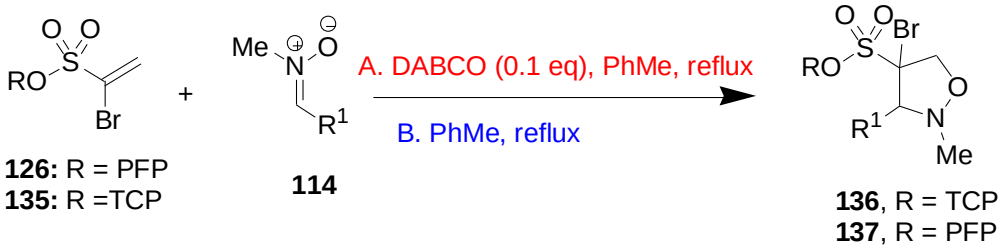


Scheme 58. Possible catalysis of the 1,3-dipolar cycloaddition.

Table 12. Results obtained from Scheme 58.

Entry	Base (0.1eq)	Yield (%)
1	-	73
2	DABCO	72
3	NEt_3	74
4	DBU	63
5	Piperidine	67

Next, the effect of base on the 1,3-dipolar cycloaddition of brominated vinyl sulfonate **126** and brominated vinyl sulfonate **135** and a range of nitrones **114** and **118** were investigated. The two reactions, with base - method **A** and without - method **B**, were carried out in parallel.



126: R = PFP
135: R =TCP

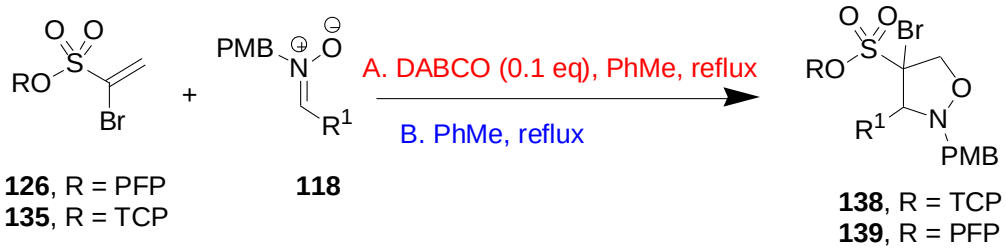
114

136, R = TCP
137, R = PFP

Scheme 59. Effect of base on the cycloaddition reaction using *N*-Me nitrone **114**.

Table 13. Results obtained from Scheme 59.

Entry	Product No	R^1	Method A (%)	Method B (%)
1	**136a**	Ph	72	78
2	**136b**	*p*-MeO.C_6H_4	65	70
3	**136c**	*p*-Cl.C_6H_4	81	82
4	**137a**	Ph	70	69
5	**137b**	*p*-MeO.C_6H_4	72	71
6	**137c**	*p*-Br.C_6H_4	76	71



126, R = PFP
135, R = TCP

118

138, R = TCP
139, R = PFP

Scheme 60

Table 14. Results obtained from Scheme 60.

Entry	Product No	R^1	Method A (%)	Method B (%)
1	**138a**	Ph	58*	70*
2	**138b**	*p*-MeO.C_6H_4	73	75
3	**138d**	$C_{10}H_7$	54*	30*
4	**139a**	Ph	65*	67*
5	**139b**	*p*-MeO.C_6H_4	75	72
6	**139d**	*p*-Br.C_6H_4	75	65

*diastereoisomers observed

The reactions with DABCO were generally successful and gave good yields overall. However, there were great inconsistencies with the yields obtained. In some reactions, the yield obtained from the reaction with DABCO was much higher than the reaction without (Table 14, entry 6), while in other cases, the reaction without DABCO gave the better yield (Table 14, entry 1).

It was now imperative to assign the diastereoisomer from the cycloaddition reaction and X-ray crystallographic analysis of a typical example **137a** confirmed that this was the *trans*-isomer (Figure 15).

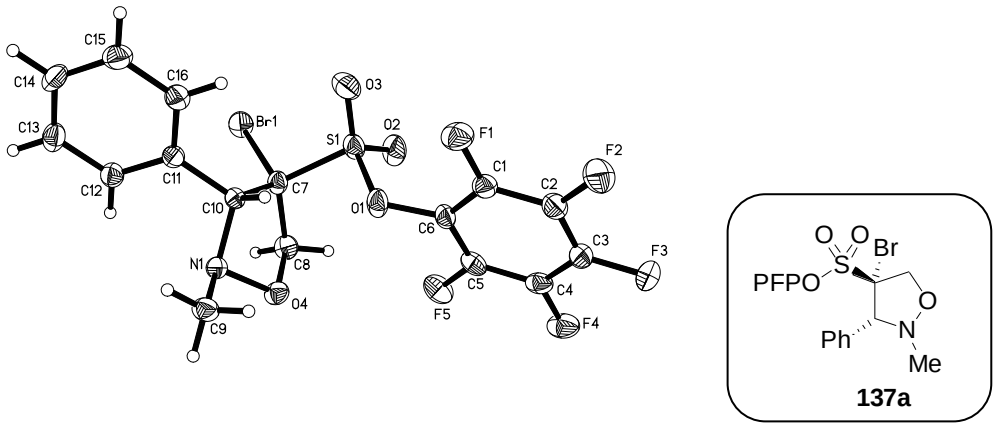
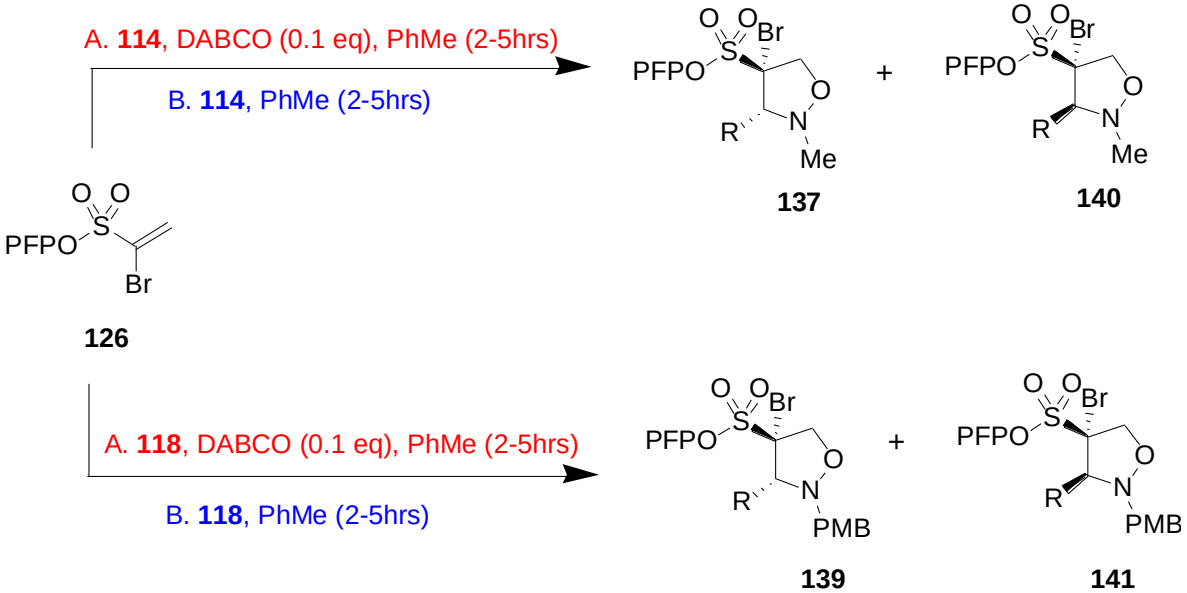


Figure 14. X-ray crystallography of isoxazolidine **137a**.

3.4.2.1 Cycloaddition reaction of α-Br PFP/TCP vinyl sulfonate at RT

The results obtained from the addition of catalytic base at 110 °C were inconclusive as there was only a slight difference in the yields between the reactions of brominated vinyl sulfonate and nitrone (Table 13 and 14). The initial reaction by Mok with PFP vinyl sulfonate **118** and nitrone indicated an improvement at room temperature (Section 3.4); therefore the cycloaddition reaction was carried out with (Method **A**) and without (Method **B**) DABCO at room temperature (Scheme 62/ Table 15).



Scheme 61. 1,3-Dipolar cycloaddition reaction at RT.

Table 15. Results obtained from Scheme 61.

Entry	R	R_1	Yield A (%)/ (137/140)*	Yield B (%)/ (137/140)*
1	Me	Ph	71 (3:1)	67 (3:2)
2	Me	*p*-MeO.C_6H_4	70 (3:1)	64 (3:1)
3	Me	*p*-Br.C_6H_4	77 (3:1)	74 (1:3)
Entry	**R**	**R_1**	**Yield A (%)/ (139/141)***	**Yield B (%)/ (139/141)***
4	PMB	Ph	65 (2:1)	66 (2:1)
5	PMB	*p*-Br.C_6H_4	37 (3:1)	20 (2:1)

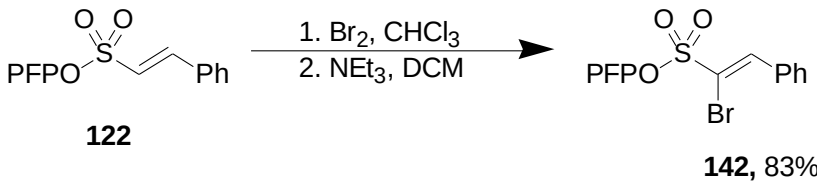
* determined by ^{1}H NMR spectroscopic analysis

The cycloaddition reaction at room temperature was successful in producing an overall good yield of brominated isoxazolidines. The reaction time varied for each nitrone used with *N*-Me nitrones **114** proceeding more rapidly. The reactions produced two inseparable diastereoisomers and NMR analysis of the peaks attributable to major isomer confirmed it to be identical to that derived for reaction of vinyl sulfonate **126** and nitrone **114** at reflux (section 3.4.1). In all reactions of the reactions, there was also the starting α-bromo vinyl sulfonate **126** isolated which varied for each reaction. The isolated diastereoisomers were the 4C regioisomer which still followed predicted behaviour of electron deficient dipolarophiles.

3.4.3 Cycloaddition with α-Br, β-Ph vinyl sulfonate

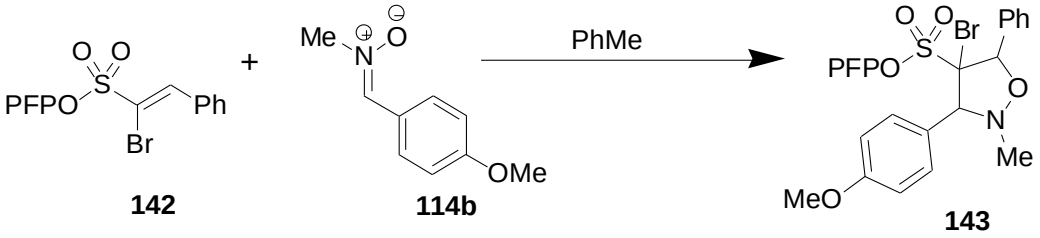
The reactivity of the β-phenyl vinyl sulfonate **122** was modified by incorporating bromine into the α position in order to evaluate the effect on its reactivity as a

dipolarophile. The synthesis of this substrate **142** was carried out using previously established procedure (Section 3.3.1) in excellent yield, 83%.



Scheme 62. Synthesis of PFP vinyl sulfonate **142**.

Initial studies on the cycloaddition reaction of α-Br,β-Ph vinyl sulfonate **142** were carried out using nitrone **114b** (Scheme 63).



Scheme 63. 1,3-Dipolar cycloaddition reaction using vinyl sulfonate **142**.

Table 16. Results obtained from Scheme 63.

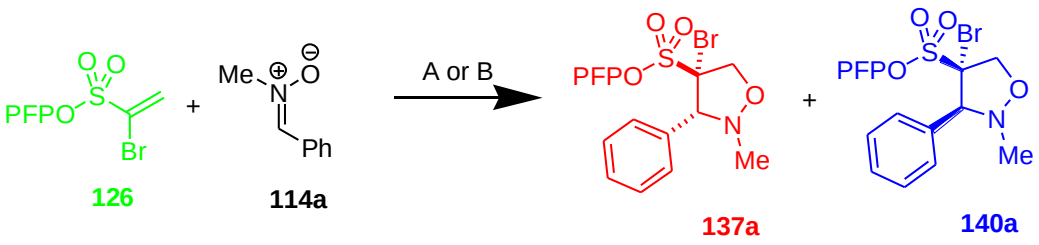
Temp (°C)	**Time**	**Yield** (%)
110	7 hrs	SM recovered
110	18 hrs	SM recovered
50	72 hrs	3
23	7 days	SM recovered

It was quite disappointing that the reaction did not give a better yield than 3%; however analysis of the NMR spectrum showed that the product was obtained with excellent regio- and stereo-selectivity. The regioisomers were assigned from the analysis of the NMR spectrum as the 4C isomer; however it has not been possible to assign the relative stereochemistry.

3.4.4 NMR Experiments on the cycloaddition reaction

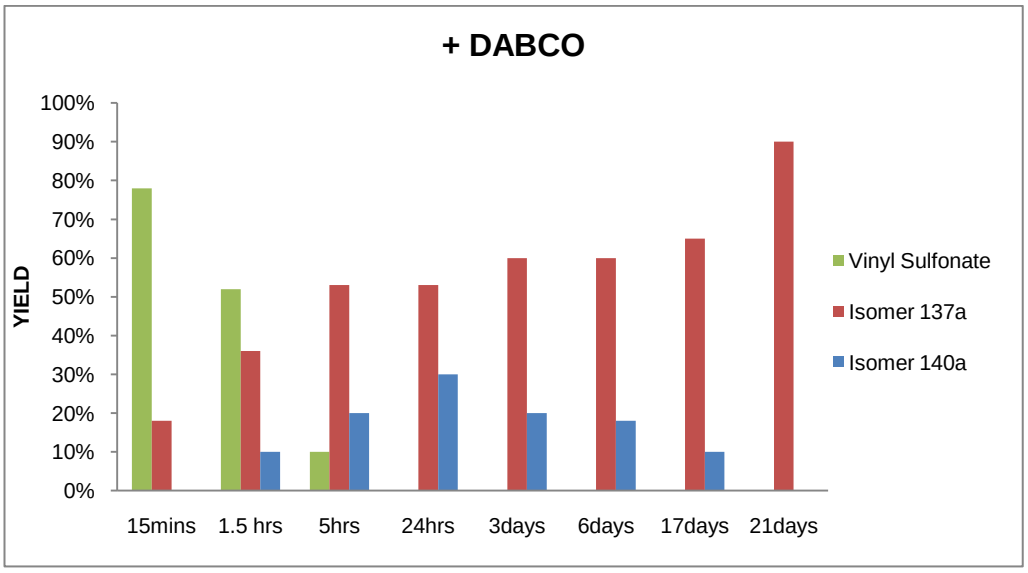
NMR monitored reactions were carried out to analyse the reaction time and products of the cycloaddition reactions. These NMR monitored reactions were carried out at room temperature as the cycloaddition reactions at RT were slower and any intermediate formed could be monitored. An internal standard, 1,4-dioxane, was used to allow yields to be determined by the integration of the 1H NMR spectrum (Scheme 64 and 65).

From the reactions with DABCO, it was observed that the initial isomer formed was *trans* isomer **137** with the formation of *cis* isomer **140** following 90 minutes later (Graphs 1 and 3). After 24 hours, the concentration of *cis* isomer **140** peaked at its highest although it was still the minor isomer with a ratio of 2:1 **137:140**. After three weeks, there was a change in the ratio with *trans* isomer **137** being the major product. The reactions without DABCO showed *cis* isomer **140** being the major product initially (Graphs 2 and 4). After 24 hours, *cis* isomer **140** was still the major isomer with a ratio of 2.5:1 **140:137**; however there was a change in ratio with *trans* isomer **137** becoming the major product after 3 weeks. In all cases, the starting vinyl sulfonate **126** is consumed in parallel with the formation of the products however, with the exception of the reaction with DABCO (Graph 1), the starting material is not completely consumed and remains in the reaction.

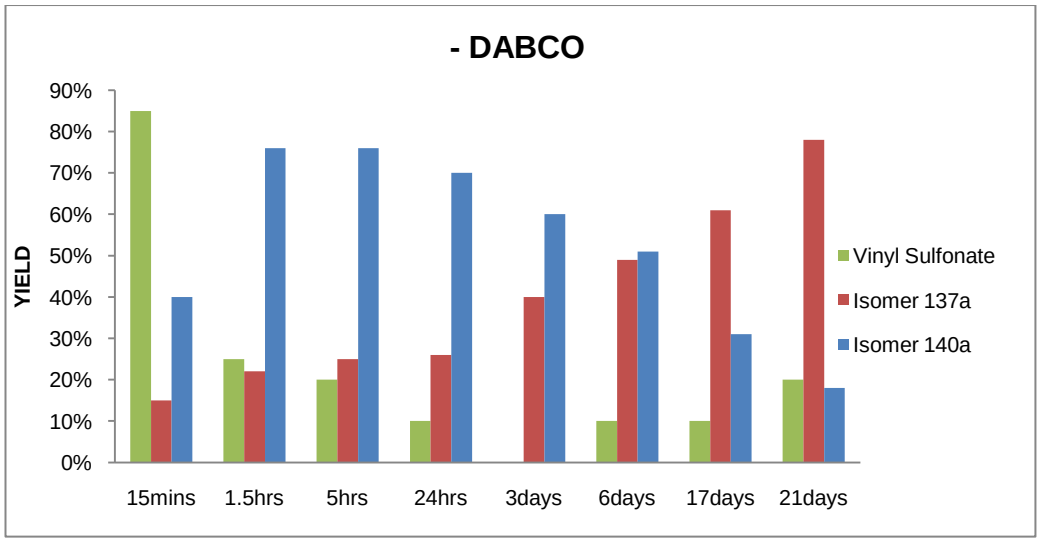


A: DABCO (0.1 eq), 1,4-dioxane (0.5 eq), d_6-benzene, RT
B: 1,4-dioxane (0.5 eq), d_6-benzene, RT

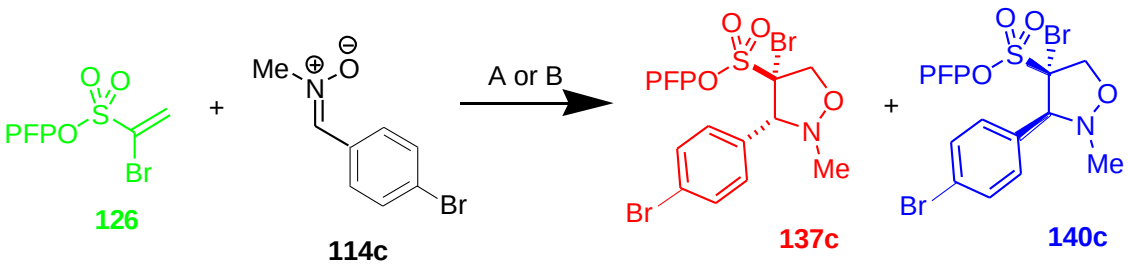
Scheme 64



Graph 1

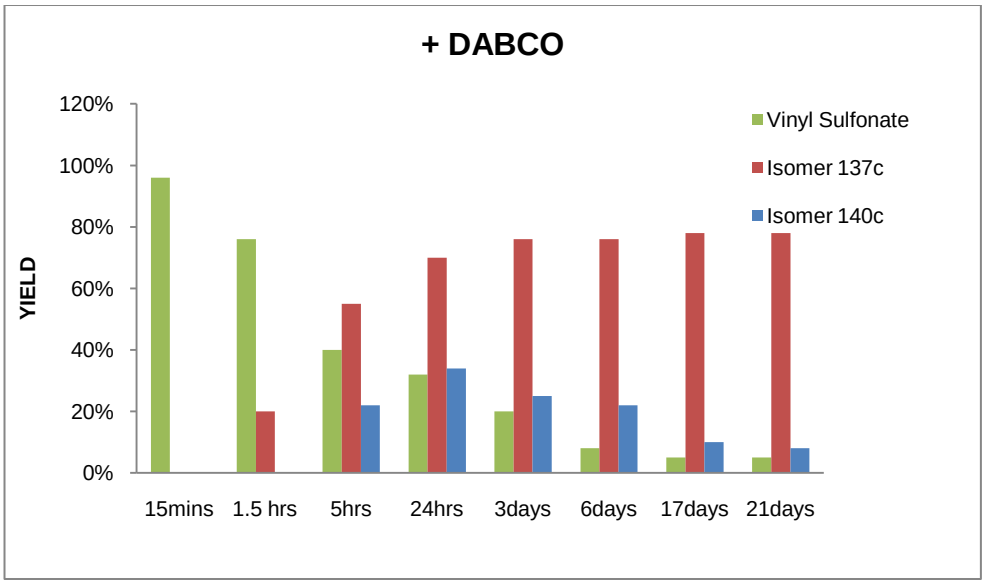


Graph 2

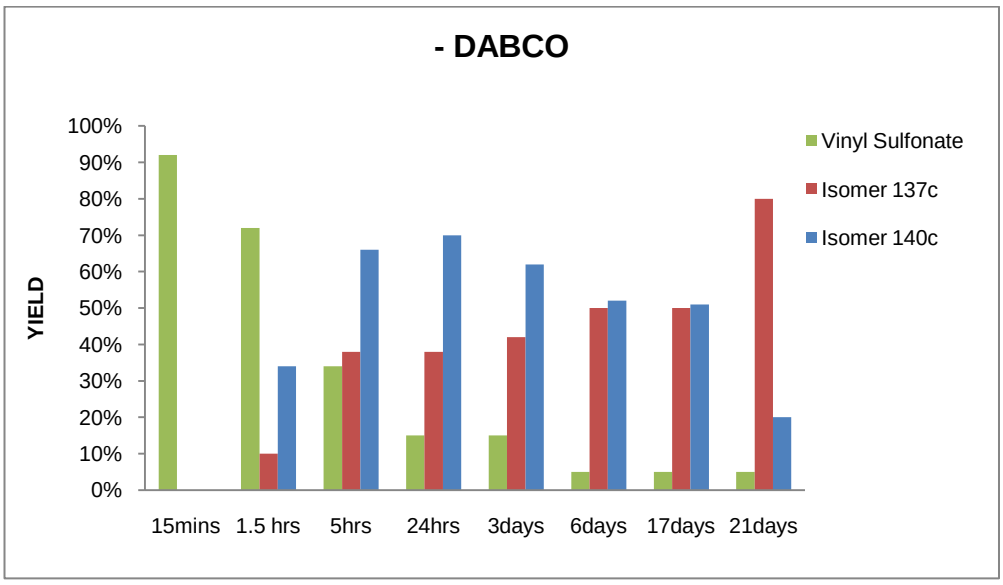


A: DABCO (0.1 eq), 1,4-dioxane (0.5 eq), d_6-benzene, RT
B: 1,4-dioxane (0.5 eq), d_6-benzene, RT

Scheme 65

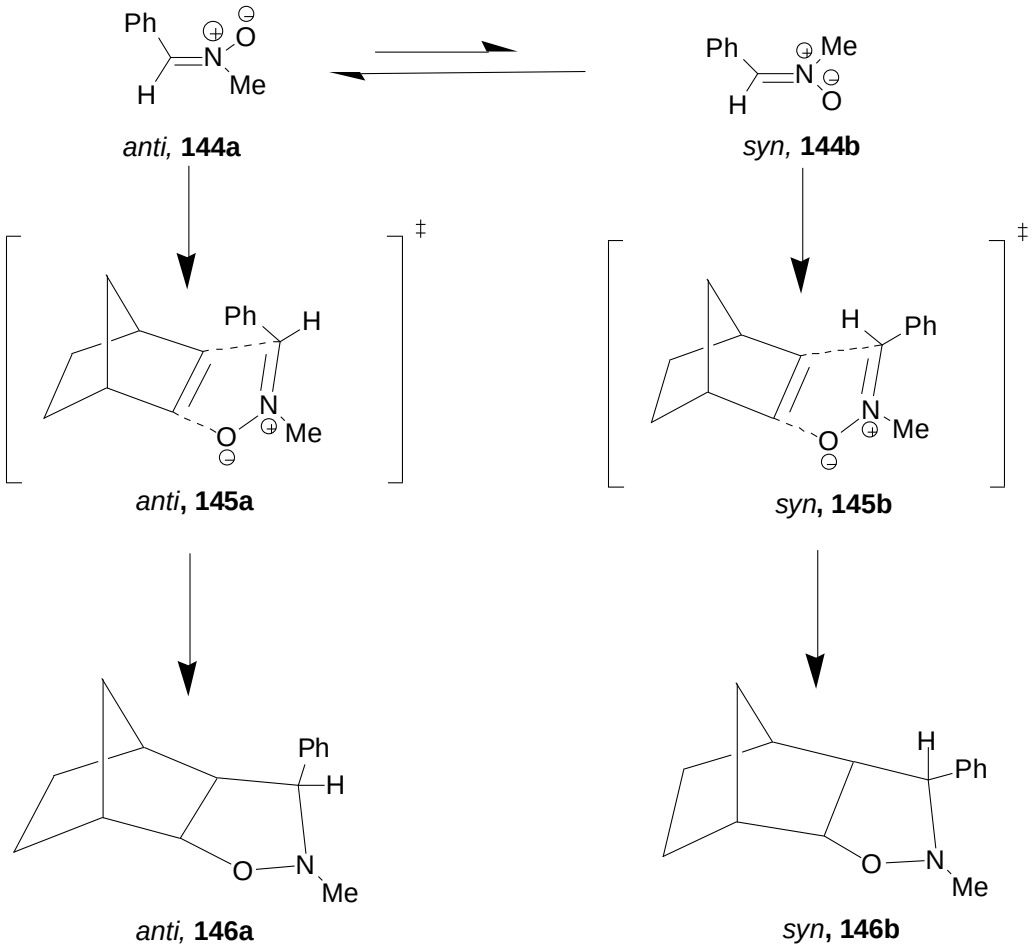


Graph 3



Graph 4

One rationale to explain why *cis* isomer **140** was formed first can be seen in the report by Boyle *et al*. It was noted in 1971 by Boyle *et al.*[83] that nitrones derived from aromatic aldehydes possessed a configuration in which the *C*-aryl and *N*-alkyl groups are in a *trans* relationship. However, formation of *cis* and *trans* adducts led them to examine for the first time the possibility that the *trans*-form of their nitrone, **144a**, was in equilibrium with a small amount of the *cis*-form, **144b**, and that the two transition states – **145a** and **145b** leading to *cis* and *trans* adducts were accessible (Scheme 66).



Scheme 66. *Trans* and *cis* nitrone in equilibrium.

They were able to conclude after further research that the favoured transition state for their nitrone was the one in which substituents are *cis* and the predominant adduct was the *cis* adduct. The existence of the *cis*-form of the nitrone therefore accounts for the formation of the *cis*-isomer **133**, however this isomer must be unstable due to steric hindrance and decomposes by cycloreversion. This cycloreversion could account for the observation of α-bromo vinyl sulfonate and aldehyde (from

decomposed nitrone) starting materials isolated after column chromatography. It was still unclear however why the reactions with DABCO gave the *trans* isomer as the major product even from the onset of the reaction, and this is an area that still needs further investigation.

3.5 Summary

This research has shown TCP and PFP vinyl sulfonates as excellent dipolarophiles for 1,3-dipolar cycloaddition. Their reactions with nitrones are both regio- and diastereo-specific producing isoxazolidines in good yields. Extending the chemistry of the vinyl sulfonates by carrying out cycloadditions with β-substituted vinyl sulfonates was also successful. The isoxazolidines were also produced regio- and diastereo-selectively although the relative stereochemistry was not confirmed.

Installing a leaving group, Br on the vinyl sulfonate did not change the reactivity of the vinyl sulfonates as a dipolarophile and cycloaddition of this species successfully generated 4C-*anti*-isoxazolidines as single diastereoisomers at reflux temperature, with inseparable diastereoisomers formed at room temperature. Catalysis of the reaction by addition of bases was not conclusive as there was only a slight improvement on the yield.

3.6 Conclusions/Future Work

This thesis has demonstrated the versatile reactivity of bifunctional acceptors pentafluorophenyl and trichlorophenyl vinyl sulfonates. Trichlorophenyl vinyl sulfonate displays similar reactivity to pentafluorophenyl sulfonate. Intermolecular radical addition to trichlorophenyl vinyl sulfonate was successful and a small library of alkyl sulfonates were synthesised. The success of the intermolecular radical addition was extended to the formation of bifunctional TCP/PFP alkyl sulfonate. This bifunctional sulfonate could be used to in future to investigate the reactivity of TCP and PFP functional groups.

Cycloaddition reactions with pentafluorophenyl vinyl sulfonate and trichlorophenyl vinyl sulfonate were successful and generated regio- and distereo- selective isoxazolidines. Cycloaddition with phenyl vinyl sulfonates extends the substitution available and a small library of substituted isoxazolidines were synthesised which were also regio- and distereo- selective. Cycloaddition using α-Br PFP vinyl sulfonate was unaffected by the presence of base at high temperature. However, at low temperature there was a change in the rate of isomerisation from kinetic to thermodynamic product which could be an effect of the base.

In future work, the versatility of PFP and TCP vinyl sulfonates could be applied to the formation of seven membered rings. It is envisaged that reacting PFP or TCP vinyl sulfonate with a diamine would result in a seven membered ring being formed *via* a Michael addition to the vinylic portion of the sulfonate followed by displacement of the PFP/TCP group.

Overall, this research has shown vinyl sulfonates are suitable precursors for the formation of a variety of alkyl and cyclic sulfonates which are amenable for further manipulations.

Chapter 4 Experimental

4.1 General Experimental

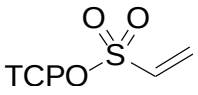
All reagents were purchased from Aldrich or AlfaAesar and were used as received without further purification unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254μm). Flash column chromatography was carried out with Kiesegel 60M 0.04/0.063mm (200-400 mesh) silica gel.

4.2 Instrumentation

^{1}H NMR spectra were recorded at 300 MHz, 400 MHz, 500 MHz and 600 MHz and ^{13}C NMR at 75 MHz, 100 MHz, 125 MHz and 150 MHz on a Bruker AMX300, AMX400, AMX500 and AMX600 respectively at ambient temperature as described below. The chemical shifts (δ) for ^{1}H and ^{13}C are quoted relative to residual signals of the solvent on the ppm scale. Coupling constants (*J* values) are reported in Hertz (Hz). Multiplicities for ^{1}H NMR are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) and multiplet (m); or some combination of these. Multiplicities for ^{13}C NMR were determined using distortionless enhancement by phase transfer (DEPT) spectral editing technique and are reported as singlet (s), doublet (d), triplet (t), quartet (q), based on the anticipated multiplicity in a non-decoupled spectrum. For compounds bearing a pentafluorophenyl group the ^{13}C NMR signals from this group are not reported due to a high degree of C-F coupling. Mass spectra were obtained on a VG70-SE mass spectrometer. Infrared spectra were obtained on a Shimadzu FTIR-8700 Fourier Transform Infrared Spectrophotometer or Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Elemental analyses were carried out at the Department of Chemistry, University College London.

4.3 Radical addition procedures

Ethenesulfonic acid 2,4,6-trichlorophenyl ester [95]



2-Chloroethane sulfonyl chloride **97** (18.1 g, 0.11 mol) was dissolved in CH_2Cl_2 (125 mL) and cooled to -50 °C. 2,4,6-trichlorophenol **96** (20.0 g, 0.10 mol) and NEt_3 (42.2 mL, 0.30 mol) were pre-mixed in CH_2Cl_2 (25 mL) and added dropwise over 1 hour to the stirred solution of 2-Chloroethane sulfonyl chloride ensuring that the temperature remains below 0 °C. The reaction was allowed to warm to 20 °C and stirred for a further 1 hour after which it was diluted with Et_2O (50 mL) and washed with 2 M HCl (50 mL) and sat. $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10-100% Et_2O in Petroleum ether 40-60 °C) to yield the title compound **95** as a white solid (15.7 g, 0.05 mol, 54%).

MP	50.5 – 51.0 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*); 6.93 (1 H, dd, *J* = 9.9 Hz, 16.6 Hz, C*H*), 6.58 (1 H, dd, *J* = 0.8 Hz, 16.6 Hz, C*H*H), 6.23 (1 H, dd, *J* = 0.8 Hz, 9.9 Hz, CH*H*).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 141.9 (s), 133.1 (d), 131.4 (s), 130.8 (t), 129.2 (d), 129.1 (d).
IR (neat)	2852 (br, -CH), 1562 (s, C=C), 1377 (s, S=O) cm^{-1}.
LRMS (CI)	288 [$(M+H)^+$, ^{37}Cl, 96%], 286 [$(M+H)^+$, ^{35}Cl, 94%], 199, [16], 197, [14].
HRMS (CI)	calcd for $C_8H_6Cl_3O_3S$ $(M+H)^+$ 286.9103, found 286.9104.

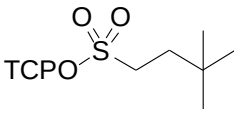
Procedure A: Radical addition using EPHP

To a solution of ethenesulfonic acid 2,4,6-trichlorophenyl ester **95** (1 mmol) and EPHP **57** (7 mmol) in CH_2Cl_2 (10 mL/mmol) was added the alkyl halide (2 mmol) and the solution was cooled to 0 °C. Et_3B (1 mmol) was added and a syringe filled with air was passed through the reaction. After 5 mins, the reaction mixture was diluted with Et_2O (20 mL/mmol), washed with 2M HCl (15 mL/mmol) and sat. aqueous $NaHCO_3$ (15 mL/mmol). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10-50% Et_2O in petroleum ether 40-60 °C).

Procedure B: Radical addition using Bu_3SnH

To a solution of ethenesulfonic acid 2,4,6-trichlorophenyl ester **95** (1 mmol) in dry toluene (30 mL/mmol) was added AIBN (20 mg/mmol) and the alkyl halide (3 mmol) and the solution was heated to 110 °C. Tri-*n*-butyltin hydride (2.5 mmol) was added dropwise over 20 mins and the reaction heated for a further 2 hours. Potassium fluoride (3.0 g/mmol) was added and the resulting suspension stirred vigorously for 16 hours. The suspension was filtered through Celite® and the filterate concentrated *in vacuo*. The crude product was purified by flash column chromatography (10-100% Et_2O in petroleum ether 40-60 °C).

3,3-Dimethylbutane-1-sulfonic acid 2,4,6-trichlorophenyl ester [98a]

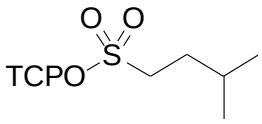


Using procedure A to afford the title compound **98a** as a white solid (190 mg, 0.55 mmol, 64%);

Using procedure B to afford the title compound **98a** as a white solid (440 mg, 1.28 mmol, 74%);

MP	91.0 – 92.0 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.41 (2 H, s, Ar*H*), 3.53 (2 H, m, CH_2), 1.97 (2 H, m, CH_2), 0.99 (9 H, s, (CH_3)$_3$).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 132.9 (s), 130.7 (s), 129.2 (d), 51.2 (t), 36.6 (t), 30.3 (s), 28.9 (q). (1 x s not observed).
IR (neat)	2923 (s, -CH), 2852 (s, -CH), 1558 (w, C=C), 1460 (s), 1377 (s, S=O) cm^{-1}.
LRMS (EI)	346 [$M^{+\cdot}$, ^{37}Cl, 15%], 344 [$M^{+\cdot}$, ^{35}Cl, 13%], 198 [100], 167 [25].
HRMS (EI)	calcd for $C_{12}H_{15}Cl_3O_3S$ ($M^{+\cdot}$) 343.9807, observed 343.9802.

3-Methylbutane-1-sulfonic acid 2,4,6-trichlorophenyl ester [98b]



Using procedure A to give the title compound **98b** as a colourless oil (180 mg, 0.55 mmol, 63%);

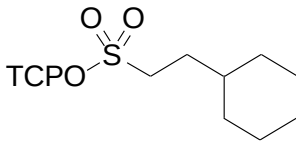
Using procedure B to give the title compound **98b** as a colourless oil (430 mg, 1.30 mmol, 74%);

^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.39 (2 H, s, Ar*H*), 3.49 (2 H, m, CH_2), 1.94 (2 H, m, CH_2), 1.83 (1 H, sept, *J* = 6.6 Hz, C*H*), 0.99 (6 H, d, *J* = 6.6 Hz, (CH_3)$_2$).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 142.1 (s), 132.9 (s), 130.7 (s), 129.2 (d), 52.8 (t), 31.9 (t), 27.3 (d), 22.0 (q).
IR (neat)	3080 (m, -CH), 2960 (s, -CH), 1560 (s, C=C), 1443 (s), 1383 (s, S=O) cm^{-1}.

LRMS (EI) 332 [$M^{+\cdot}$, ^{37}Cl, 23%], 330 [$M^{+\cdot}$, ^{35}Cl, 21%], 196 [100], 169 [20].

HRMS (EI) calcd for $C_{11}H_{13}Cl_3O_3S$ ($M^{+\cdot}$) 329.9651, observed 329.9646.

2-Cyclohexylethanesulfonic acid 2,4,6-trichlorophenyl ester [98c]



Using procedure A to give the title compound **98c** as a white solid (230 mg, 0.62 mmol, 72 %);

Using procedure B to give the title compound **98c** as a white solid (470 mg, 1.26 mmol, 72 %);

MP 60.0 – 61.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*), 3.65 (2 H, m, CH_2), 1.99 (2 H, m, CH_2), 1.72 (4 H, m, 2 x CH_2), 1.25 (1 H, m, C*H*), 1.23 (4 H, m, 2 x CH_2), 0.99 (2 H, m, CH_2).

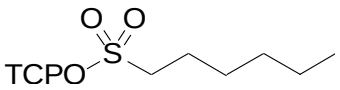
^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (s), 130.7 (s), 129.2 (d), 52.5 (t), 36.6 (d), 32.8 (t), 30.2 (t), 26.3 (t), 25.9 (t). (1 x s not observed).

IR (neat) 2922 (s, -CH), 2852 (s, -CH), 1562 (m), 1445 (s), 1379 (s, S=O) cm^{-1}.

LRMS (EI) 372 [$M^{+\cdot}$, ^{37}Cl, 18%], 370 [$M^{+\cdot}$, ^{35}Cl, 16%], 196 [100], 169 [22].

HRMS (EI) calcd for $C_{14}H_{15}Cl_3O_3S$ ($M^{+\cdot}$) 369.99639, observed 369.99563.

Hexane-1-sulfonic acid 2,4,6-trichlorophenyl ester [98d]

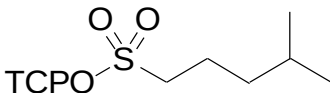


Using procedure A to give the title compound **98d** as a light yellow oil (150 mg, 0.44 mmol, 51%);

Using procedure B to give the title compound **98d** as a clear oil (320 mg, 0.92 mmol, 53%);

^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*), 3.55 (2 H, t, *J* = 8.0 Hz, CH_2), 2.05 (2 H, m, CH_2), 1.56 (2 H, m, CH_2), 1.37 (4 H, m, 2 x CH_2), 0.93 – 0.88 (3 H, m, CH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 142.1 (s), 132.9 (s), 130.7 (s), 129.2 (d), 54.3 (t), 31.1 (t), 27.9 (t), 23.6 (t), 22.3 (t), 13.9 (q).
IR (neat)	2920 (s, -CH), 2890 (s, -CH), 1552 (m), 1440 (s, C=C), 1378 (s, S=O) cm^{-1}.
LRMS (EI)	346 [$M^{+\cdot}$, ^{37}Cl, 15%], 344 [$M^{+\cdot}$, ^{35}Cl, 13%], 196 [100].
HRMS (EI)	calcd for $C_{12}H_{15}Cl_3O_3S$ ($M^{+\cdot}$) 343.9807, observed 343.9802.

4-Methylpentane-1-sulfonic acid 2,4,6-trichlorophenyl ester [98e]

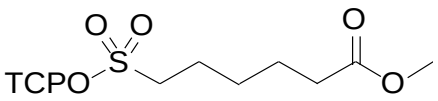


Using procedure A to give the title compound **98e** as a light yellow oil (100 mg, 0.29 mmol, 33%);

Using procedure B to give the title compound **98e** as a clear oil (390 mg, 1.13 mmol, 65%);

^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.51 (2 H, s, Ar*H*), 3.52 (2 H, t, *J* = 8.0 Hz, CH_2), 2.06 (2 H, m, CH_2), 1.63 (1 H, sept, *J* = 6.7 Hz, C*H*), 1.40 (2 H, m, CH_2), 0.99 (6 H, d, *J* = 6.7 Hz, (CH_3)$_2$).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 142.1 (s), 132.9 (s), 130.7 (s), 129.2 (d), 54.5 (t), 37.3 (t), 27.7 (d), 22.3 (q), 21.6 (t).
IR (neat)	2957 (m, -CH), 2872 (w), 1558 (s, C=C), 1443 (s, C=C), 1383 (s, S=O) cm^{-1}.
LRMS (EI)	346 [$M^{+\cdot}$, ^{37}Cl, 15%], 344 [$M^{+\cdot}$, ^{35}Cl, 13%], 196 [100].
HRMS (EI)	calcd for $C_{12}H_{15}Cl_3O_3S$ ($M^{+\cdot}$) 343.9807, observed 343.9798.

6-(2,4,6-Trichlorophenoxysulfonyl)-hexanoic acid methyl ester [98h]



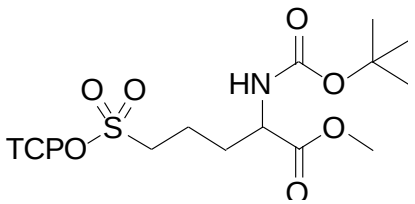
Using procedure B to give the title compound **98h** as a light yellow oil (340 mg, 0.94 mmol, 50%);

^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*), 3.67 (3 H, s, CH_3), 3.55 – 3.50 (2 H, m, CH_2), 2.36 (2 H, t, *J* = 7.2 Hz, CH_2), 2.05 – 2.15 (2 H, m, CH_2), 1.76 – 1.66 (2 H, m, CH_2), 1.62 – 1.52 (2 H, m, CH_2).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 173.6 (s), 142.0 (s), 132.9 (s), 130.6 (s), 129.2 (d), 54.0 (t), 51.6 (q), 33.5 (t), 27.6 (t), 24.2 (t), 23.4 (t).
IR (neat)	2928 (s, -CH), 2855 (s, -CH), 1732 (s, C=O), 1560 (m), 1445 (s, C=C), 1375 (s, S=O) cm^{-1};
LRMS (CI-Methane)	391 [$(M+CH_3)^+$, ^{35}Cl, 10%], 359 [60], 181 [30], 163 [75],

131 [35].

HRMS (CI-Methane) calcd for $C_{13}H_{15}Cl_3O_5S$ $(M+H)^+$ 356.98857, observed 356.98985.

2-tert-Butoxycarbonylamino-5-(2,4,6-trichlorophenoxysulfonyl)-pentanoic acid methyl ester [98f]



Using procedure B to give the title compound **98f** as a white solid (320 mg, 0.64 mmol, 37 %);

MP 67.0 – 68.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (2 H, s, Ar*H*), 5.15 (1 H, d, *J* = 7.6 Hz, N*H*), 4.56 – 4.19 (1 H, m, C*H*), 3.76 (3 H, s, CH_3), 3.57 (2 H, apparent q, CH_2), 2.23 – 1.79 (4 H, m, 2 x CH_2), 1.43 (9 H, s, (CH_3)$_3$).

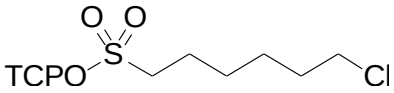
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (s), 141.9 (s), 133.0 (s), 130.6 (s), 129.2 (d), 65.8 (t), 53.5 (t), 52.6 (d), 50.4 (q), 31.2 (t), 28.3 (q). (2 x s not observed).

IR (neat) 3369 (m), 2853 (br, -CH), 1732 (m, C=O), 1678 (m, C=O), 1518 (m, C=C), 1456 (s, C=C), 1377 (s, S=O) cm^{-1}.

LRMS (FAB) 514 [$(M+Na)^+$, ^{35}Cl, 85%]

HRMS (FAB) calcd for $C_{17}H_{22}Cl_3NNaO_7S$ $(M+Na)^+$ 513.78308, observed 513.78298.

6-Chlorohexane-1-sulfonic acid 2,4,6-trichlorophenyl ester [101b]

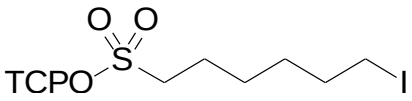


Using procedure B to yield the title compound **101b** as a colourless oil (342.5 mg, 0.905 mmol, 52%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*), 3.56 – 3.46 (4 H, m, 2 x C*H*$_2$), 2.19 – 2.08 (2 H, m, C*H*$_2$), 1.86 – 1.79 (2 H, m, C*H*$_2$), 1.62 – 1.47 (4 H, m, 2 x C*H*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (s), 130.7 (s), 129.2 (d), 128.8 (d), 123.8 (s), 49.8 (t), 45.0 (t), 33.1 (t), 27.7 (t), 26.8 (t), 23.4 (t).

6-Iodohexane-1-sulfonic acid 2,4,6-trichlorophenyl ester [102b]

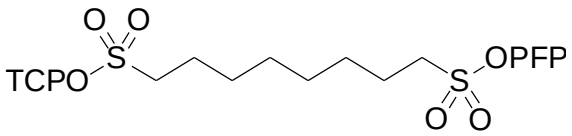


6-Chlorohexane-1-sulfonic acid 2,4,6-trichlorophenyl ester **101b** (1.04 g, 2.75 mmol) was dissolved in acetone (30 mL) and sodium iodide (0.78 g, 5.50 mmol) was added in portions and the reaction heated to 56 °C and stirred for 48 hours. The mixture was filtered and the white solid residue was washed with acetone. The filtrate was concentrated *in vacuo* to obtain a yellowish solid to which was added Et_2O. The organic layer was filtered and concentrated to obtain the title compound **102b** as a light yellow solid (0.94 g, 2.12 mmol, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*), 3.56 – 3.41 (2 H, m, C*H*$_2$), 3.13 – 3.09 (2 H, m, C*H*$_2$), 1.86 – 1.79 (4 H, m, 2 x C*H*$_2$), 1.62 – 1.47 (4 H, m, 2 x C*H*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (s), 130.7 (s), 129.2 (d), 128.8 (d), 123.8 (s), 49.8 (t), 34.0 (t), 30.4 (t), 27.3 (t), 23.4 (t).

Octane-1,8-disulfonic acid pentafluorophenyl ester 2,4,6-trichlorophenyl ester [103b]

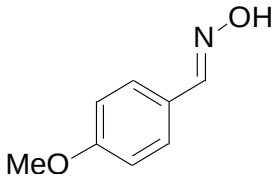


To a solution of ethenesulfonic acid pentafluorophenyl ester **85** (260 mg, 0.95 mmol) in dry toluene (30 mL) was added AIBN (20 mg) and 6-iodohexane-1-sulfonic acid 2,4,6-trichlorophenyl ester **102b** (0.89 g, 1.89 mmol) and the solution heated to 110 °C. Tri-*n*-butyltin hydride (0.64 mL, 2.38 mmol) was added dropwise over 20 mins and the reaction heated for a further 2 hours. Potassium fluoride (3.0 g) was added and the resulting suspension stirred vigorously for 16 hours. The suspension was filtered through celite and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (10 – 100% Et_2O in petroleum ether 40 – 60 °C) to generate the title compound **103b** as a white solid (390 mg, 0.63 mmol, 66%).

MP	89.0 – 91.0 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.40 (2 H, s, Ar*H*), 3.55 (2 H, t, *J* = 7.7 Hz, CH_2), 3.44 (2 H, t, *J* = 7.7 Hz, CH_2), 2.14 – 1.99 (4 H, m, 2 x CH_2), 1.60 – 1.42 (8 H, m, 4 x CH_2).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 142.1 (s), 132.9 (s), 130.6 (s), 129.2 (d), 54.2 (t), 28.6 (t), 28.0 (t), 27.9 (t), 23.6 (t), 23.5 (t), 23.5 (t).
IR (neat)	2924 (s, -CH), 2853 (s, -CH), 1518 (m), 1464 (s, C=C), 1377 (s, S=O) cm^{-1}.
LRMS (FAB)	643 [$(M+Na)^+$, ^{35}Cl, 20%], 553 [10], 499 [10], 360 [20].
HRMS (FAB)	calcd for $C_{12}H_{15}Cl_3NaO_3S$ $(M+Na)^+$ 640.9428, observed 640.94344.

4.4 Nitrone Procedures[81]

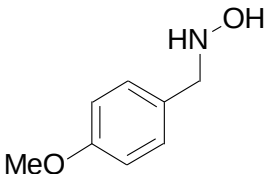
4-Methoxy benzaldehyde oxime [116]



Hydroxylamine hydrochloride (20.0 g, 0.26 mol) and triethylamine (69.7 mL, 0.49 mol) was added to a stirred solution of anisaldehyde (20.0 g, 0.15 mmol) in CH_2Cl_2 (500 mL) and the reaction was stirred at 25 °C for 2 hrs after which it was cooled in an ice-bath. $NaHCO_3$ (200 mL) was added to the cooled mixture and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL) and the organic layers were combined together and concentrated *in vacuo* to yield the crude which was purified by flash chromatography (10-100% EtOAc in petroleum ether 40-60 °C) to afford the title compound **116** as a white solid (22.0 g, 0.15 mol, 99%).

MP	72-74 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 9.22 (br s, 1 H, O*H*), 8.13 (s, 1 H, C*H*N), 7.52 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 3.82 (s, 3 H, OCH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 161.1 (s), 150.0 (d), 128.6 (d), 124.6 (s), 114.3 (d), 55.4 (q).
IR (neat)	3170 (br, -OH), 2839 (w), 1607 (s, C=N), 1512 (s, C=C), 1441 (w), 1250 (s) cm^{-1}.
LRMS (CI)	152 [$(M+H)^+$, 100%].
HRMS (CI)	calcd for $C_8H_{10}NO_2$ $(M+H)^+$ 152.0712, found 152.0708.

N-(4-Methoxybenzyl)-hydroxylamine [117]



Concentrated HCl (7 mL) was added to a stirred solution of 4-methoxy benzaldehyde oxime **116** (5.00 g, 33.1 mmol) and $NaBH_3CN$ (4.10 g, 66.2 mmol) in MeOH (50 mL) at 0 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 4 hrs. 6 M KOH was added until pH was approximately 9 and the reaction mixture was concentrated *in vacuo*. The crude was then extracted with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **117** as a yellowish solid (3.63 g, 23.7 mmol).

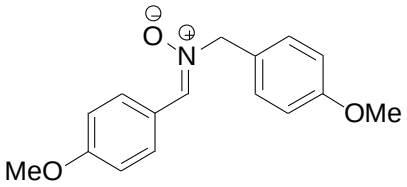
MP	80.0-82.0 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.12 (br s, 1 H, N*H*), 3.91 (s, 2 H, CH_2NH), 3.78 (s, 3 H, OCH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 159.2 (s), 130.5 (d), 128.9 (s), 113.9 (d), 57.6 (t), 55.3 (q).
IR (neat)	3210 (br, -OH), 2837 (w), 1610 (s), 1511 (s), 1250 (s) cm^{-1}.
LRMS (EI)	153 [$M^{+\cdot}$, 90%].
HRMS (EI)	calcd for $C_8H_{11}NO_2$ ($M^{+\cdot}$) 153.0784, found 153.0795.

Procedure C: Formation of *N*-(4-methoxybenzyl) nitrones [118]

To a stirring solution of *N*-(4-methoxybenzyl)-hydroxylamine **117** (1.0 mol) in CH_2Cl_2 (30 mL/mol) was added the corresponding aldehyde (1.5 mol) and $MgSO_4$ (2.0 mol). The mixture was stirred at 40 °C overnight, then the resulting suspension was filtered and the resulting residue was washed thoroughly with CH_2Cl_2 (2 x 50

mL/mol). The combined organic fractions were concentrated *in vacuo* to yield a solid that was recrystallised (EtOAc/petroleum ether 40-60 °C) to give the title compound.

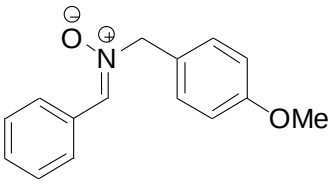
_N_-(4-Methoxybenzyl)-_N_-(4-methoxyphenyl) methylidene amine oxide [118a]



Using procedure C to yield a white solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **118a** as a white solid (1.30 g, 4.9 mmol, 75%).

MP	127-129 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 7.37 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.25 (s, 1 H, C*H*N), 6.90 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 4.92 (s, 2 H, NCH_2Ar), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 161.1 (s), 160.1 (s), 133.6 (d), 130.9 (d), 130.6 (d), 125.5 (s), 123.5 (s), 114.3 (d), 113.7 (d), 70.1 (t), 55.3 (q).
IR (neat)	3007 (w), 2837 (w), 1603 (s, C=N), 1512 (s, C=C), 1239 (s), 1025 (s) cm^{-1}.
LRMS (EI)	271 [$M^{+\cdot}$, 12%], 121 [100], 91 [31].
HRMS (EI)	calcd for $C_{16}H_{17}NO_3$ ($M^{+\cdot}$) 271.1203, found 271.1208.

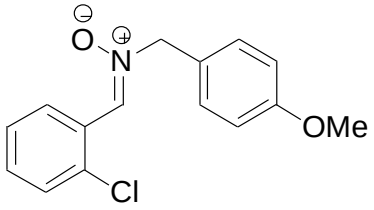
N-(4-Methoxybenzyl)-*N*-phenylmethylidene amine oxide [118c][81]



Using procedure C to yield a white solid that was recrystallised (EtOAc/petroleum ether 40-60 °C) to give the title compound **118c** as white crystals (1.10 g, 4.7 mmol, 72%):

MP	96-97 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 8.18-8.21 (m, 2 H, Ar*H*), 7.38-7.42 (m, 5 H, Ar*H*), 7.33 (s, 1 H, C*H*N), 6.93 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.99 (s, 2 H, CH_2N), 3.82 (s, 3 H, OCH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 160.2 (s), 133.8 (d), 130.9 (d), 130.5 (s), 130.4 (d), 128.6 (d), 128.4 (d), 125.3 (s), 114.4 (d), 70.7 (t), 55.4 (q).
IR (neat)	3051 (w), 2934 (w), 1610 (s, C=N), 1514 (s, C=C), 1250 (s), 1026 (s) cm^{-1}.
LRMS (FAB)	264 [$(M+Na)^+$, 48%], 199 [63], 173 [100].
HRMS (FAB)	calcd for $C_{15}H_{15}NO_2Na$ $(M+Na)^+$ 264.1000, found 264.1004.

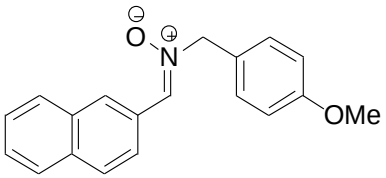
_N_-(2-Chlorophenyl) methylidene-_N_-(4-methoxybenzyl)amine oxide [118b]



Using procedure C to yield a white solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **118b** as a white solid (1.20 g, 4.9 mmol, 65%).

MP	142-144 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 9.32-9.26 (m, 1 H, Ar*H*), 7.89 (s, 1 H, C*H*N), 7.46-7.25 (m, 5 H, Ar*H*), 6.94 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.02 (s, 2 H, NCH_2Ar), 3.82 (s, 3 H, OCH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 132.7 (s), 131.0 (d), 129.4 (d), 129.0 (d), 128.1 (s), 127.1 (d), 113.0 (d), 55.3 (q).
IR (neat)	3007 (w), 2837 (w), 1612 (s, C=N), 1513 (s, C=C), 1238 (s), 1031 (s) cm^{-1}.
LRMS (EI)	277 [$M^{+\cdot}$,^{37}Cl, 4%], 275 [$M^{+\cdot}$,^{35}Cl, 12%], 121 [100], 89 [41].
HRMS (EI)	calcd for $C_{15}H_{14}ClNO_2$ ($M^{+\cdot}$) 275.0708, found 275.0711.

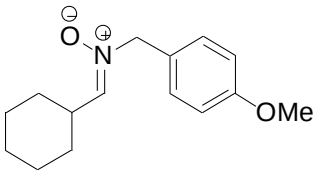
N-(4-Methoxybenzyl)-*N*-naphthalen-2-ylmethylidene amine oxide [118e]



Using procedure C to yield a white solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **118e** as a cream solid (2.60 g, 8.9 mmol, 92%).

MP	155-158 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 9.22 (s, 1 H, C*H*N), 7.78-7.91 (m, 4 H, Ar*H*), 7.47-7.51 (m, 3 H, Ar*H*), 7.44 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.95 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.03 (s, 2 H, NCH_2Ar), 3.82 (s, 3 H, OCH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 135.3 (d), 134.1 (s), 133.1 (s), 129.2 (d), 128.4 (d), 128.0 (d), 127.8 (s), 127.6 (d), 127.4 (d), 126.5 (d), 125.7 (d), 54.5 (q).
IR (neat)	3053 (w), 2932 (w), 1610 (s, C=N), 1514 (s, C=C), 1249 (s), 1021 (s) cm^{-1}.
LRMS (EI)	291 [$M^{+\cdot}$, 38], 275 [15], 139 [40], 121 [100].
HRMS (EI)	calcd for $C_{19}H_{17}NO_2$ ($M^{+\cdot}$) 291.1254, found 291.1260.

N-Cyclohexylmethylidene-*N*-(4-methoxybenzyl)amine oxide [118d]



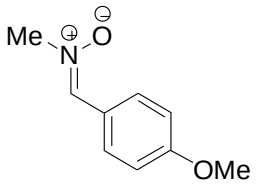
Using procedure C to yield a white solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **118d** as a white solid (1.10 g, 4.4 mmol, 60%).

MP	92-95 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.38 (d, *J* = 7.2 Hz, 1 H, C*H*N), 4.77 (s, 2 H, NCH_2Ar), 3.79 (s, 3 H, OCH_3), 2.88-3.01 (m, 1 H, C*H*CHN), 1.76-1.86 (m, 2 H, cyclohexyl-*H*), 1.58-1.70 (m, 3 H, cyclohexyl-*H*), 1.01-1.41 (m, 5 H, cyclohexyl-*H*).
^{13}C NMR	(300 MHz, $CDCl_3$) δ 144.2 (d), 52.6 (q), 44.2 (d), 28.7 (t), 25.8 (t), 25.1 (t).
IR (neat)	3063 (w), 2924 (s, CH), 1612 (s, C=N), 1513 (s, C=C), 1238 (s), 1031 (s) cm^{-1}.
LRMS (EI)	247 [$M^{+\cdot}$, 8%], 230 [16], 121 [100], 91 [33].
HRMS (EI)	calcd for $C_{15}H_{21}NO_2$ ($M^{+\cdot}$) 247.1567, found 247.1561.

Procedure D: Formation of *N*-methyl nitrones [114]

To a stirring solution of *N*-methylhydroxylamine (1.5 mol) in CH_2Cl_2 (30 mL/mol) was added benzaldehyde (1.0 mol) and $MgSO_4$ (3.0 mol). The mixture was stirred at 40 °C for 2 hours. The resulting suspension was filtered and the resulting residue was washed thoroughly with CH_2Cl_2 (2 x 50 mL/mol). The combined organic fractions were concentrated *in vacuo* to yield a solid that was recrystallised (EtOAc/petroleum ether 40-60 °C) to give the title compound.

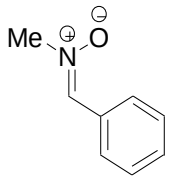
_N_-(4-Methoxyphenyl) methylidene-_N_-methylamine oxide [114b]



Using procedure D to yield a white solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **114b** as a white solid (11.0 g, 0.07 mol, 67%).

MP	81 - 82 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 8.20 (m, 2 H, Ar*H*), 7.29 (s, 1 H, C*H*), 6.92 (m, 2 H, Ar*H*), 3.86 (s, 6 H, 2 x CH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 161.0 (s), 135.0 (d), 130.4 (d), 123.4 (s), 113.8 (d), 55.6 (q), 53.9 (q).
IR (neat)	3399 (w), 3007 (w), 2840 (w), 1601 (s, C=N), 1506 (s, C=C), 1412 (s) cm^{-1}.
LRMS (EI)	165 [$M^{+\cdot}$, 100%].
HRMS (EI)	calcd for $C_9H_{11}NO_2$ ($M^{+\cdot}$) 165.0790, found 165.0791.

N-Methyl-*N*-phenylmethylidene amine oxide [114a]



Using procedure D to yield a white solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **114a** as a white solid (10.0 g, 0.07 mol, 70%).

MP 89-91 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.20 (m, 2 H, Ar*H*), 7.44 – 7.40 (m, 3 H, Ar*H*), 7.37 (s, 1 H, C*H*), 3.87 (s, 3 H, CH_3).

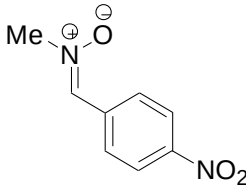
^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3 (d), 130.5 (s), 130.4 (d), 128.7 (d), 128.4 (d), 54.4 (q).

IR (neat) 3058 (w), 1601 (s, C=N), 1594 (s, C=C), 1405 (s) cm^{-1}.

LRMS (EI) 135 [$M^{+\cdot}$, 99%].

HRMS (EI) calcd for C_8H_9NO ($M^{+\cdot}$) 135.0684, found 135.0682.

N-Methyl-*N*-(4-nitrophenyl) methylidene amine oxide [114c]



Using procedure D to yield an orange solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **114c** as a yellow-orange solid (3.75 g, 24.9 mmol, 50 %).

MP 218-220 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 8.27 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 8.10 (s, 1 H, C*H*), 3.85 (s, 3 H, C*H*3).

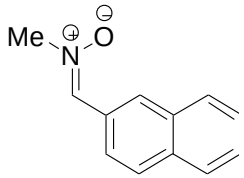
^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9 (s), 136.7 (s), 132.7 (d), 128.3 (d), 123.7 (d), 54.7 (q).

IR (neat) 3055 (w), 2986 (w), 1594 (s, NO_2), 1423 (s) cm^{-1}.

LRMS (EI) 180 [$M^{+\cdot}$, 100%].

HRMS (EI) calcd for $C_8H_8N_2O_3$ ($M^{+\cdot}$) 180.0535, found 180.0526.

N-Methyl-*N*-naphthalen-2-ylmethylidene amine oxide [114d]



Using procedure D to yield a cream solid that was recrystallised (EtOAc in petroleum ether 40-60 °C) to give the title compound **114d** as a white solid (3.12 g, 19.9 mmol, 80 %).

MP 127-128 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1 H, C*H*), 7.94 – 7.80 (m, 4 H, Ar*H*), 7.54 – 7.47 (m, 3 H, Ar*H*), 3.90 (s, 3 H, C*H*3).

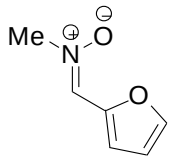
^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3 (d), 134.1 (s), 133.1 (s), 129.2 (d), 128.4 (d), 128.0 (d), 127.8 (s), 127.6 (d), 127.4 (d), 126.5(d), 125.7 (d), 54.5 (q).

IR (neat) 2995 (w), 1576 (s, C=C), 1402 (s) cm^{-1}.

LRMS (EI) 185 [$M^{+\cdot}$, 100%].

HRMS (EI) calcd for $C_{12}H_{11}NO$ ($M^{+\cdot}$) 185.0841, found 185.0844.

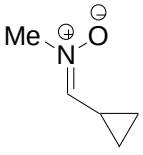
N-Furan-2-ylmethylidene-*N*-methylamine oxide [114e]



Using procedure D to yield a brown solid that was recrystallised (EtOAc/petroleum ether 40-60 °C) to give the title compound **114e** as brown needles (1.96 g, 16.2 mmol, 65%).

MP	96-98 °C.
^{1}H NMR	(300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 3.5 Hz, 1 H, C*H*O), 7.53 (s, 1 H, C*H*N), 7.45 (d, *J* = 1.7 Hz, 1 H, C*H*CO), 6.53 – 6.52 (m, 1 H, OCHC*H*CH), 3.80 (s, 3 H, CH_3).
^{13}C NMR	(75 MHz, $CDCl_3$) δ 148.1 (s), 143.7 (d), 126.4 (d), 115.5 (d), 112.4 (d), 52.7 (q).
IR (neat)	3140 (w), 1596 (s, C=C), 1483 (s), 1401 (s), 1229 (s) cm^{-1}.
LRMS (EI)	125 [$M^{+\cdot}$, 98%].
HRMS (EI)	calcd for $C_6H_7NO_2$ ($M^{+\cdot}$) 125.0477, found 125.0479.

N-Cyclopropylmethylidene-*N*-methylamine oxide [114f]



Using procedure D to yield a yellow oil as the title compound **114f** (1.58 g, 15.9 mmol, 80%).

^{1}H NMR	(300 MHz, $CDCl_3$) δ 6.07 (d, *J* = 8.5 Hz, 1 H, C*H*N), 3.56 (s, 3 H, CH_3), 2.18-2.30 (m, 1 H, C*H*(CH_2)$_2$), 0.92-0.99 (m, 2 H, CH_2CH),

0.57-0.60 (m, 2 H, CH_2CH).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 (d), 51.8 (q), 9.3 (d), 6.9 (t), 6.6 (t).

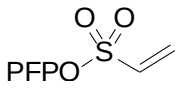
IR (neat) 3007 (w), 1630 (s, C=N), 1402 (s), 1227 (s), 1134 (s) cm^{-1}.

LRMS (EI) 99 [$M^{+\cdot}$, 68%].

HRMS (EI) calcd for C_5H_9NO ($M^{+\cdot}$) 99.0684, found 99.0690.

4.5 1,3-Dipolar cycloaddition procedures

Ethenesulfonic acid pentafluorophenyl ester [85]



2-Chloroethanesulfonyl chloride (5.7 mL, 0.054 mol) was dissolved in CH_2Cl_2 (75 mL) and cooled to -10 °C. Pentafluorophenol (10.0 g, 0.054 mol) and NEt_3 (22.7 mL, 0.163 mol) were pre-mixed in CH_2Cl_2 (25 mL) and added dropwise over 1 hour to the stirred solution of 2-chloroethanesulfonyl chloride ensuring that the temperature remains below 0 °C. The reaction was allowed to warm up to room temperature and stirred for a further 1 hour after which it was diluted with Et_2O (50 mL) and washed with 2M HCl (50 mL) and sat. $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to yield the title compound **85** as a light yellow oil (8.90 g, 0.032 mol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 – 6.55 (1 H, m, C*H*), 6.42 (1 H, dd, *J* = 0.6 Hz, 17.1 Hz, C*H*H), 6.29 (1 H, dd, *J* = 0.6 Hz, 9.8 Hz, CH*H*).

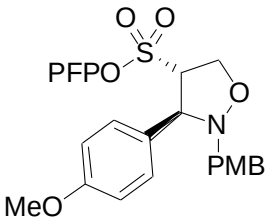
^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 (s), 133.2 (d), 131.7 (d).

IR (neat) 3123 (w), 3080 (w), 1522 (s, C=C), 1393 (s, S=O) cm^{-1}.

LRMS (EI) 274 [$M^{+\cdot}$, 33%, 184 [76], 136 [38], 117 [25], 105 [17], 91 [77], 27 [100].

HRMS (EI) calcd for $C_8H_3F_5O_3S$ (M^+) 273.9723, found 273.9727.

2-(4-Methoxybenzyl)-3-(4-Methoxybenzyl)-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [119a]



To ethenesulfonic acid pentafluorophenyl ester **85** (200 mg, 0.74 mmol) in dry toluene (5 mL) was added *N*-(4-methoxybenzyl)-*N*-(4-methoxyphenyl) methylidene amine oxide 118a (200 mg, 0.74 mmol) and DABCO (8.0 mg, 0.074 mmol) and the mixture was stirred at reflux for 3 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **119a** as a yellow solid (380 mg, 0.70 mmol, 93%).

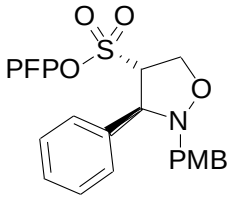
MP 118-119 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.47-7.39 (m, 3 H, Ar*H*), 7.26 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 4.61 (dd, *J* = 10.4, 2.4 Hz, 1 H, SCHC*H*H), 4.42-4.49 (m, 1 H, SCHCH*H*), 4.29-4.36 (m, 2 H, SC*H* and NC*H*), 3.97 (d, *J* = 14.2 Hz, 1 H, NC*H*HAr), 3.82 (d, *J* = 14.2 Hz, 1 H, NCH*H*Ar), 3.78 (s, 3 H, CH_3), 3.64 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (s), 159.1 (s), 136.2 (s), 130.2 (d), 129.1 (d), 128.5 (s), 114.5 (d), 113.7 (d), 73.6 (d), 71.4 (d), 66.9 (t), 58.8 (t), 55.2 (q), 54.4 (q).

IR (neat) 3007 (w), 2837 (w), 1612 (s), 1513 (s, C=C), 1238 (s), 1031 (s) cm^{-1}.

2-(4-Methoxybenzyl)-3- phenyl isoxazolidine-4-sulfonic acid pentafluoro phenyl ester [119b]



To ethenesulfonic acid pentafluorophenyl ester **85** (230 mg, 0.83 mmol) in dry toluene (5 mL) was added *N*-(4-methoxybenzyl)-*N*-phenylmethylidene amine oxide **118c** (200 mg, 0.83 mmol) and the mixture was stirred at reflux for 3 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **119b** as a white solid (310 mg, 0.61 mmol, 72%).

MP 88-92 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.56 (m, 2 H, Ar*H*), 7.36-7.45 (m, 3 H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.61 (dd, *J* = 10.4, 2.4 Hz, 1 H, SCHC*H*H), 4.42-4.49 (m, 1 H, SCHCH*H*), 4.29-4.36 (m, 2 H, SC*H* and NC*H*), 3.97 (d, *J* = 14.2 Hz, 1 H, NC*H*HAr), 3.82 (d, *J* = 14.2 Hz, 1 H, NCH*H*Ar), 3.78 (s, 3 H, OCH_3).

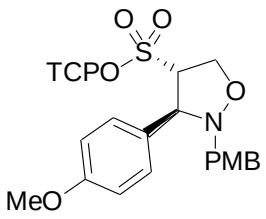
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (s), 136.2 (s), 130.2 (d), 129.1 (d), 128.5 (s), 128.1 (d), 113.7 (d), 73.6 (d), 71.4 (d), 66.9 (t), 58.8 (t), 55.2 (q).

IR (neat) 2957 (w), 1513 (s, C=C), 1468 (w), 1249 (s), 1020 (s) cm^{-1}.

LRMS (FAB) 516 [$(M+H)^+$, 10%], 154 [100].

HRMS (FAB) calcd for $C_{23}H_{19}F_5NO_5S$ $(M+H)^+$ 516.0904, found 516.0900.

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [120a]



To ethenesulfonic acid 2,4,6-trichlorophenyl ester **95** (200 mg, 0.70 mmol) in dry toluene (5 mL) was added *N*-(4-methoxybenzyl)-*N*-(4-methoxyphenyl) methylidene amine oxide **118a** (190 mg, 0.70 mmol) and DABCO (8.0 mg, 0.07 mmol) and the mixture was stirred at reflux for 3 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound as a white solid (230 mg, 0.42 mmol, 60%).

MP 59-60 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 9.3Hz, 2 H, Ar*H*), 7.36 (s, 2 H, Ar*H*), 7.23 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 6.94 (d, *J* = 8.97 Hz, 2 H, Ar*H*), 6.82 (d, *J* = 8.77, 2 H, Ar*H*), 4.61 (m, 1 H, SC*H*CHH), 4.42-4.49 (m, 2 H, SCHC*HH*), 4.29-4.36 (m, 1 H, SCHC*H*), 3.97 (d, *J* = 13.8 Hz, 1 H, NC*H*HAr), 3.82 (d, *J* = 13.8 Hz, 1 H, NCH*H*Ar), 3.78 (s, 6 H, 2 x C*H*$_3$).

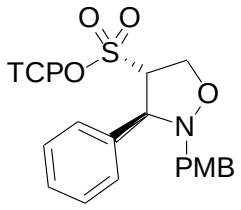
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (s), 159.3 (s), 141.2 (s), 136.6 (s), 129.1 (d), 128.8 (d), 123.8 (s), 114.2 (d), 113.7 (d), 73.6 (d), 71.4 (d), 66.9 (t), 56.9 (t), 55.2 (q), 55.1 (q).

IR (neat) 2930 (w), 2836 (w), 1737 (w), 1611 (m), 1561 (m), 1511 (s, C=C), 1440 (s, C=C), 1383 (s, S=O).

LRMS (EI) 559 [$M^{+\cdot}$, ^{37}Cl, 89%], 557 [$M^{+\cdot}$, ^{35}Cl 87%].

HRMS (EI) calcd for $C_{24}H_{21}Cl_3NO_3S$ (M^+) 557.01784, found 557.01877.

2-(4-Methoxybenzyl)-3-phenyl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [120b]



To ethenesulfonic acid 2,4,6-trichlorophenyl ester **95** (200 mg, 0.70 mmol) in dry toluene (5 mL) was added *N*-(4-methoxybenzyl)-*N*-phenylmethylidene amine oxide **118c** (170 mg, 0.70 mmol) and DABCO (8.0 mg, 0.07 mmol) and the mixture was stirred at reflux for 3 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **120b** as a white solid (270 mg, 0.51 mmol, 75%).

MP 50-51 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.34 (s, 2 H, Ar*H*), 7.41-7.32 (m, 3 H, Ar*H*), 7.24 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.8 Hz, 2 H, ArH), 4.61 (d, *J* = 6.7 Hz, 1 H, SC*H*), 4.44-4.55 (m, 2 H, SCHC*HH*), 4.39 (d, *J* = 6.7 Hz, 1 H, NC*H*), 3.91 (d, *J* = 13.6 Hz, 1 H, NC*H*HAr), 3.82 (d, *J* = 13.6 Hz, 1 H, NCH*H*Ar), 3.78 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (s), 141.7 (s), 136.7 (s), 133.2 (s), 130.5 (d), 130.2 (d), 129.2 (d), 129.1 (d), 128.8 (d), 128.2 (d), 123.8 (s), 113.8 (d) 74.7 (d), 71.7 (d), 67.3 (t), 58.9 (t), 55.3 (q). (1 x s not observed).

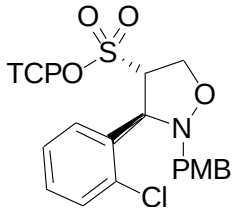
IR (neat) 2253 (w), 1613 (m), 1561 (m), 1513 (s, C=C), 1441 (s, C=C),

1386 (s, S=O) cm^{-1}.

LRMS (EI) 529 [$M^{+\cdot}$, ^{37}Cl, 5%], 527 [$M^{+\cdot}$, ^{35}Cl, 3%], 121 [100].

HRMS (EI) calcd for $C_{23}H_{20}Cl_3NO_5S$ (M^+) 527.01223, found 527.01168.

3-(2-Chlorophenyl)-2-(4-methoxybenzyl)-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [120c]



To ethenesulfonic acid 2,4,6-trichlorophenyl ester **95** (200 mg, 0.70 mmol) in dry toluene (5 mL) was added *N*-(2-chlorophenyl) methylidene-*N*-(4-methoxybenzyl)amine oxide **118b** (190 mg, 0.70 mmol) and DABCO (8.0 mg, 0.07 mmol) and the mixture was stirred at reflux for 3 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **120c** as a white waxy solid (190 mg, 0.34 mmol, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.41-7.19 (m, 6 H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.98 (d, *J* = 6.96 Hz, 1 H, SC*H*CHH), 4.73-4.49 (m, 3 H, SCHC*H*C*HH*), 3.91 (d, *J* = 13.6 Hz, 1 H, NC*H*HAr), 3.82 (d, *J* = 13.6 Hz, 1 H, NCH*H*Ar), 3.78 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (s), 141.8 (s), 134.7 (s), 133.9 (s), 133.2 (s), 130.5 (s), 130.4 (d), 130.1 (d), 130.0 (d), 129.2 (d), 128.7 (d),127.5 (d), 113.8 (d), 73.9 (d), 67.6 (t), 59.1 (t), 55.3 (d), 31.0 (q).

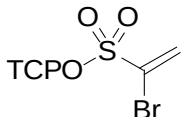
IR (neat) 2930 (w), 2836 (w), 1737 (w), 1611 (m), 1561 (m), 1511 (s, C=C),

1440 (s, C=C), 1383 (s, S=O).

LRMS (EI) 563 [$M^{+\cdot}$, ^{37}Cl, 5%], 561 [$M^{+\cdot}$, ^{35}Cl, 3%].

HRMS (EI) calcd for $C_{23}H_{19}Cl_4NO_5S$ (M^+) 560.97326, found 560.97326.

1-Bromo-ethenesulfonic acid 2,4,6-trichlorophenyl ester [135]



Bromine (4.5 mL, 87.5 mmol) in $CHCl_3$ (30 mL) was added dropwise to a stirring suspension of TCP vinyl sulfonate **95** (12.0 g, 43.8 mmol) and AIBN (0.5 g) in $CHCl_3$ (150 mL). After addition, AIBN was added (0.50 g) and the reaction mixture stirred at reflux for 4 hours, followed by 40 hours at 20 °C. The solvent was removed *in vacuo* and the crude oil remaining re-suspended in CH_2Cl_2 (100 mL). To this stirring solution was added NEt_3 (9.2 mL, 65.7 mmol) and the reaction stirred at 20 °C for 3 hrs. The reaction mixture was washed with 2M hydrochloric acid (100 mL), the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **135** as a white solid (14.0 g, 38.2 mmol, 87%).

MP 54 -56 °C

^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (2 H, s, ArH), 7.02 (1 H, d, *J* = 3.5 Hz, C*H*H), 6.44 (1 H, d, *J* = 3.5 Hz, CH*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1 (s), 133.5 (s), 131.4 (t), 130.8 (s), 129.5 (d), 121.7 (s).

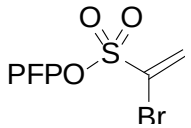
IR (neat) 3114 (w), 3081 (w), 3029 (w), 1561 (s, C=C), 1439 (s, C=C), 1390 (s, S=O) cm^{-1}.

LRMS (EI) 371 [$M^{+\cdot}$, ^{81}Br, ^{37}Cl, 5%], 369 [$M^{+\cdot}$, ^{79}Br, ^{37}Cl, 25%], 367 [$M^{+\cdot}$, ^{81}Br, ^{35}Cl, 45%], 365 [$M^{+\cdot}$, ^{79}Br, ^{35}Cl, 15%], 195 [100], 167 [40],

117 [90].

HRMS (EI) calcd for $C_8H_4Cl_3O_3S^{79}Br$ ($M^{+\cdot}$) 364.81246, found 364.81281.

1-Bromo-ethenesulfonic acid pentafluorophenyl ester [126]



Bromine (5.6 mL, 0.11 mol) in $CHCl_3$ (50 mL) was added dropwise to a stirring suspension of ethenesulfonic acid pentafluorophenyl ester **85** (16.0 g, 0.055 mol) and AIBN (1.30 g) in $CHCl_3$ (150 mL). After addition, another equivalent of AIBN was added (1.30 g) and the reaction mixture stirred at reflux for 4 hours, followed by 40 hours at 20 °C. The solvent was removed *in vacuo* and the crude oil remaining re-suspended in toluene (150 mL). To this stirring solution was added NEt_3 (7.7 mL, 0.055 mol) and the reaction stirred at 20 °C for 3 hrs. The reaction mixture was washed with 2M HCl (2 x 50 mL), the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **126** as yellow oil (15.0 g, 0.043 mol, 77%);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 3.5 Hz, 1 H, SCC*H*H), 6.54 (d, *J* = 3.5 Hz, 1 H, SCCH*H*).

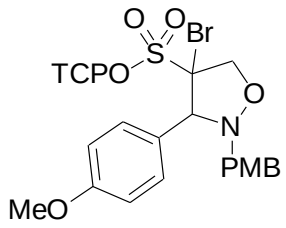
^{13}C NMR (75 MHz, $CDCl_3$) δ 133. 8 (t), 122.0 (s).

IR (neat) 3025 (w), 1555 (s, C=C), 1430 (s, C=C), 1391 (s, S=O) cm^{-1}

LRMS (EI) 354 [$M^{+\cdot}$, ^{81}Br, 10%], 352 [$M^{+\cdot}$, ^{79}Br, 8%], 184 [100], 155 [47], 117, [53], [69 [37].

HRMS (EI) calcd for $C_8H_2{}^{79}BrF_5O_3S$ (M^+) 351.8823, found 351.8827.

4-Bromo-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [138b]



1-Bromoethenesulfonic acid 2,4,6-trichlorophenyl ester **135** (200 mg, 0.55 mmol) and DABCO (6.2 mg, 0.055 mmol) was dissolved in PhMe (5 mL) and stirred at 20 °C for 5 mins, then treated with *N*-(4-methoxybenzyl)-*N*-(4-methoxyphenyl) methylidene amine oxide **118a** (180 mg, 0.66 mmol). The resulting suspension was stirred at reflux for 2.5 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O /petroleum ether 40-60 °C) to give the title compound **138b** as a white solid and a single diastereoisomer (250 mg, 0.39 mmol, 71%):

MP 54.0 – 55.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (2 H, d, *J* = 9.1 Hz, Ar*H*), 7.43 (2 H, s, Ar*H*), 7.24 (2 H, d, *J* = 9.1 Hz, Ar*H*), 6.96 (2 H, d, *J* = 8.8 Hz, Ar*H*), 6.85 (2 H, d, *J* = 8.8 Hz, Ar*H*), 5.25 (1 H, d, *J* = 10.7 Hz, OC*H*H), 4.73 (1 H, s, NC*H*), 4.56 (1 H, d, *J* = 10.7 Hz, OCH*H*), 4.09 (1 H, d, *J* = 14.5 Hz, NC*H*HAr), 3.84 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.77 (1 H, d, *J* = 14.5 Hz, NCH*H*Ar).

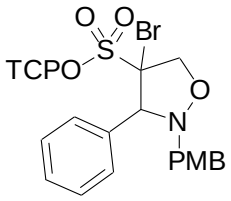
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4 (s), 159.2 (s), 140.1 (s), 133.8 (s), 131.3 (s), 130.4 (d), 129.7 (d), 128.8 (d), 128.1 (s), 126.0 (s), 114.2 (d), 113.8 (d), 83.5 (s), 80.5 (t), 74.6 (d), 58.9 (t), 55.3 (q).

IR (neat) 3071 (w), 2935 (w), 1737 (w), 1612 (m), 1512 (s, C=C), 1438 (m), 1381 (s, S=O).

LRMS (CI) 640 [$(M+H)^+$, ^{81}Br, ^{37}Cl, 5%], 638 [$(M+H)^+$, ^{81}Br, ^{35}Cl, 15%], 636 [$(M+H)^+$, ^{79}Br, ^{37}Cl, 34%], 634 [$(M+H)^+$, ^{79}Br, ^{35}Cl, 25%].

HRMS (CI) calcd for $C_{24}H_{21}{}^{79}BrCl_3NO_6S$ $(M+H)^+$ 635.93385, found 635.93379.

4-Bromo-2-(4-methoxybenzyl)-3-phenyl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [138a]



1-Bromoethenesulfonic acid 2,4,6-trichlorophenyl ester **135** (0.50 g, 1.36 mmol) and DABCO (15.0 mg, 0.136 mmol) was dissolved in PhMe (10 mL) and stirred at 20 °C for 5 mins, then treated with *N*-(4-methoxybenzyl)-*N*-phenylmethylidene amine oxide **118c** (492 mg, 2.04 mmol). The resulting suspension was stirred at reflux for 3 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **138a** as a white waxy solid as an inseparable 3:1 mixture of diastereoisomers (0.67 g, 1.10 mmol, 81%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.52 (m, 2 H, Ar*H*), 7.49 – 7.40 (m, 5 H, Ar*H*), 7.28 – 7.23 (m, 2 H, Ar*H*), 6.97 – 6.88 (m, 2 H, Ar*H*, minor), 6.88 – 6.82 (m, 2 H, Ar*H*, major), 5.28 (d, *J* = 11.0 Hz, 1 H, OC*H*H), 4.80 (s, 1 H, NC*H*, major), 4.73 (s, 1 H, NC*H*, minor), 4.68 (d, *J* = 11.0 Hz, 1 H, OCH*H*, minor), 4.58 (d, *J* = 11.0 Hz, 1 H, OCH*H*, major), 4.16 (d, *J* = 14.4 Hz, 1 H, NC*H*HAr, minor), 4.12 (d, *J* = 14.3 Hz, 1 H, NC*H*HAr, major), 3.94 (s, 3 H, OCH_3, minor), 3.80 (s, 3 H, OCH_3, major), 3.72 (d, *J* = 14.4 Hz, 1 H, NCH*H*Ar).

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3 (s), 159.2 (s), 133.8 (s), 130.3 (s), 129.6 (d), 129.2 (s), 128.8 (d), 128.6 (d), 125.8 (d), 123.8 (s), 113.7 (d), 82.9 (s), 78.0 (t), 74.5 (d), 58.9 (t), 55.2 (q).

IR (neat) 2930 (w), 1612 (m), 1560 (m), 1513 (s, C=C), 1437 (s, C=C),

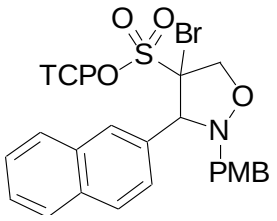
1378 (s, S=O) cm^{-1}.

LRMS (EI) 611 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, 7%], 609 [($M^{+\cdot}$, ^{81}Br, ^{35}Cl, 18%], 607 [($M^{+\cdot}$, ^{79}Br, ^{37}Cl, 25%], 605 [($M^{+\cdot}$, ^{79}Br, ^{35}Cl, 15%].

HRMS (EI) calcd for $C_{23}H_{19}{}^{79}BrCl_3NO_5S$ ($M^{+\cdot}$) 604.91778, found 604.91586.

Microanalysis Calcd C, 45.46, H, 3.15, N, 2.30; found C, 45.20, H, 3.21, N, 2.24.

4-Bromo-2-(4-methoxybenzyl)-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [138d]



1-Bromoethenesulfonic acid 2,4,6-trichlorophenyl ester **135** (0.50 g, 1.36 mmol) and DABCO (15.0 mg, 0.136 mmol) was dissolved in PhMe (5 mL) and stirred at 20 °C for 5 mins, then treated with ***N***-(4-methoxybenzyl)-***N***-naphthalen-2-ylmethylidene amine oxide **118e** (475 mg). The resulting suspension was stirred at reflux for 2 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **138d** a clear syrup as inseparable 4:1 mixture of diastereoisomers (421 mg, 0.73 mmol, 54%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1 H, Ar*H*), 7.89 – 7.82 (m, 4 H, Ar*H*, major), 7.83 – 7.81 (m, 2 H, Ar*H*, minor), 7.71 (br s, 2 H, Ar*H*, minor), 7.54 – 7.51 (m, 2 H, Ar*H*, major), 7.50 – 7.45 (m, 2 H, Ar*H*, minor), 7.27 – 7.21 (m, 4 H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 2 H, Ar*H*, minor), 6.84 (d, J = 8.6 Hz, 2 H, Ar*H*, major), 5.31 (d, J = 11.1 Hz, 1 H, C*H*HO, minor), 5.30 (d, *J* = 11.1, 1 H, C*H*HO, major), 4.95 (s, 1 H, C*H*, major), 4.87 (s, 1 H, C*H*, minor), 4.71 (d, *J* = 11.1 Hz, 1 H, CH*H*O, minor), 4.63 (d, *J* = 11.1 Hz, 1 H,

CH*H*O, major), 4.13 (d, *J* = 14.3 Hz, 1 H, NC*H*H), 3.86 (d, *J* = 14.3 Hz, 1 H, NCH*H*), 3.81 (s, 3 H, CH_3, minor), 3.78 (s, 3 H, CH_3, major).

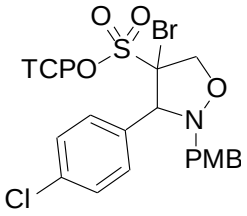
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (s), 140.2 (s), 133.9 (s), 133.0 (s), 131.8 (s), 131.0 (s), 130.5 (d), 129.7 (d), 129.5 (d), 128.5 (d), 128.1 (d), 128.0 (s), 127.9 (s), 127.8 (d), 126.9 (d), 126.5 (d), 113.8 (d), 82.9 (s), 78.1 (t), 75.0 (d), 59.1 (t), 55.3 (q).

IR (neat) 2919 (m), 1610 (m), 1555 (m), 1437 (s, C=C), 1378 (s, S=O) cm^{-1}.

LRMS (CI) 659 [$(M+H)^+$, ^{81}Br, ^{37}Cl, 1%], 657 [$(M+H)^+$, ^{81}Br, ^{35}Cl, 3%], 655 [$(M+H)^+$, ^{79}Br, ^{37}Cl, 5%], 653 [$(M+H)^+$, ^{79}Br, ^{35}Cl, 3%], 583 [10], 412 [45], 367 [60], 292 [100], 195 [15].

HRMS (CI) calcd for $C_{27}H_{21}{}^{79}BrCl_3NO_5S$ $(M+H)^+$ 654.94676, found 654.94692.

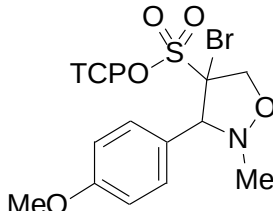
4-Bromo-3-(4-chlorophenyl)-2-(4-methoxybenzyl)isoxazolidine-4-sulfonic acid 2,4,6-trichloro-phenyl ester [138e]



1-Bromoethenesulfonic acid 2,4,6-trichlorophenyl ester **135** (0.50 g, 1.36 mmol) and DABCO (15.0 mg, 0.136 mmol) was dissolved in PhMe (20 mL) and stirred at 20 °C for 5 mins, then treated with *N*-(4-chlorophenyl) methylidene-*N*-(4-methoxybenzyl)amine oxide[81] (0.56 g, 2.04 mmol). The resulting suspension was stirred at reflux for 4 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **138e** a white solid as a single distereoisomer (440 mg, 0.69 mmol, 52%).

MP	146 – 148 °C
^{1}H NMR	(500 MHz, $CDCl_3$) δ 7.52 (2 H, d, *J* = 8.7 Hz, Ar*H*), 7.43 (2 H, s, Ar*H*), 7.41 (2 H, d, *J* = 8.8 Hz, Ar*H*), 7.23 (2 H, d, *J* = 8.8 Hz, Ar*H*), 6.84 (2 H, d, *J* = 8.7 Hz, Ar*H*), 5.25 (1 H, d, *J* = 11.0 Hz, SCBrC*H*H), 4.75 (1 H, s, SCBrC*H*N), 4.55 (1 H, d, *J* = 11.0 Hz, SCBrCH*H*), 4.08 (1 H, d, *J* = 14.5 Hz, NC*H*HAr), 3.81 (1 H, d, *J* = 14.5 Hz, NCH*H*Ar), 3.78 (3 H, s, CH_3).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 159.3 (s), 147.0 (s), 140.0 (s), 139.9 (s), 135.5 (s), 133.9 (s), 132.8 (s), 131.0 (d), 130.4 (d), 129.7 (d), 113.8 (d), 83.6 (s), 80.1 (t), 74.2 (d), 59.0 (t), 55.4 (q).
IR (neat)	2852 (br, CH), 1562 (s, C=C), 1456 (s, C=C), 1377 (s, S=O) cm^{-1}.
LRMS (EI)	645 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, ^{37}Cl, 1%], 643 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, ^{35}Cl, 2%], 641 [($M^{+\cdot}$, ^{79}Br, ^{37}Cl, ^{35}Cl, 5%], 639 [($M^{+\cdot}$, ^{79}Br, ^{35}Cl, ^{35}Cl, 5%], 366 [55], 195 [100].
HRMS (EI)	calcd for $C_{23}H_{18}{}^{79}BrCl_4NO_5S$ ($M^{+\cdot}$) 638.88377, found 638.88529.

4-Bromo-3-(4-methoxyphenyl)-2-methyl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [136b]



1-Bromo-ethenesulfonic acid 2,4,6-trichloro-phenyl ester **135** (0.50 g, 1.36 mmol) was dissolved in PhMe (5 mL) and treated with ***N***-(4-methoxyphenyl) methylidene-***N***-methylamine oxide **114b** (270 mg, 1.63 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to

give the title compound **136b** a white solid as a single diastereoisomer (0.50 g, 0.94 mmol, 70%).

MP 75 – 76 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 4 H, Ar*H*), 6.93 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 5.27 (d, *J* = 11.0 Hz, 1 H, OC*H*H), 4.60 (d, *J* = 11.0 Hz, 1 H, OCH*H*), 4.48 (s, 1 H, NC*H*), 3.82 (s, 3 H, CH_3), 2.76 (s, 3 H, CH_3).

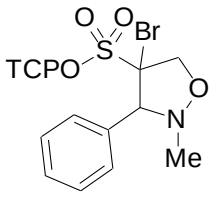
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4 (s), 140.2 (s), 133.8 (s), 131.2 (d), 129.7 (d), 129.2 (s), 125.8 (s), 113.7 (d), 83.8 (s), 78.1 (t), 77.4 (d), 55.3 (q), 43.2 (q).

IR (neat) 1611 (s, C=C), 1558 (s), 1512 (s), 1433 (s), 1383 (s, S=O), 1250 (s) cm^{-1}.

LRMS (EI) 535 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, 1%], 533 [($M^{+\cdot}$, ^{81}Br, ^{35}Cl, 2%], 531 [($M^{+\cdot}$, ^{79}Br, ^{37}Cl, 5%], 529 [($M^{+\cdot}$, ^{79}Br, ^{35}Cl, 3%], 366 [15], 195 [20], 164 [100].

HRMS (EI) calcd for $C_{17}H_{15}{}^{79}BrCl_3NO_5S$ ($M^{+\cdot}$) 528.89144, found 528.89153.

4-Bromo-2-methyl-3-phenylisoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [136a]



1-Bromoethenesulfonic acid 2,4,6-trichlorophenyl ester **135** (0.50 g, 1.36 mmol) was dissolved in PhMe (5 mL) and treated with *N*-methyl-*N*-phenylmethylidene amine oxide **114a** (220 mg, 1.63 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash

chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **136a** a white solid as a single distereoisomer (0.53 g, 1.06 mmol, 78%).

MP 79.8 – 80.0 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 7 H, Ar*H*), 5.12 (d, *J* = 11.1 Hz, 1 H, OC*H*H), 4.64 (d, *J* = 11.1 Hz, 1 H, OCH*H*), 4.41 (s, 1 H, NC*H*Ar), 2.78 (s, 3 H, NCH_3).

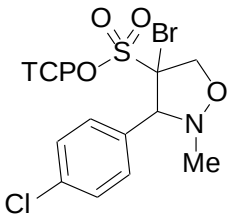
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2 (s), 134.0 (s), 131.1 (s), 130.0 (d), 129.6 (d), 129.5 (d), 128.4 (d), 123.8 (s), 83.5 (s), 78.1 (t), 77.7 (d), 43.2 (q).

IR (neat) 3077 (w), 1561 (s, C=C), 1438 (s, C=C), 1380 (s, S=O), 1223 (s), 1193 (s), 1057 (s) cm^{-1}.

LRMS (EI) 500 [$M^{+\cdot}$, 15%], 504 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, 5%], 502 [($M^{+\cdot}$, ^{81}Br, ^{35}Cl, 10%], 500 [($M^{+\cdot}$, ^{79}Br, ^{37}Cl, 15%], 498 [($M^{+\cdot}$, ^{79}Br, ^{35}Cl, 12%], 366 [15], 195 [40].

HRMS (EI) calcd for $C_{16}H_{13}NO_4SCl_3{}^{79}Br$ ($M^{+\cdot}$) 498.88088, found 498.88059.

4-Bromo-3-(4-chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [136c]

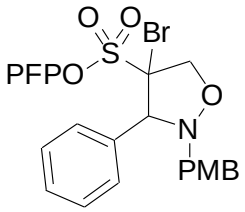


1-Bromoethenesulfonic acid 2,4,6-trichlorophenyl ester **135** (0.50 g, 1.36 mmol) was dissolved in PhMe (5 mL) and treated with ***N***-(4-chlorophenyl) methylidene-***N***-methylamine oxide[81] (280 mg, 1.63 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title

compound **136c** a white waxy solid as a single distereoisomer (150 mg, 0.28 mmol, 21%);

^{1}H NMR	(500 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 6 H, Ar*H*), 5.28 (d, *J* = 10.9 Hz, 1 H, OC*H*H), 4.59 (d, *J* = 11.0 Hz, 1 H, OCH*H*), 4.51 (s, 1 H, NC*H*Ar), 2.77 (s, 3 H, NCH_3).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 140.1 (s), 135.5 (s), 134.0 (s), 132.5 (s), 131.2 (d), 129.8 (d), 128.7 (d), 123.6 (s), 83.0 (s), 78.2 (t), 77.1 (d), 43.2 (q).
IR (neat)	3080 (w), 2878 (w), 1561 (s, C=C), 1492 (s), 1379 (s, S=O), 1222 (s), 1193 (s), 1057 (s) cm^{-1}.
LRMS (EI)	537 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, ^{37}Cl, 3%], 535 [($M^{+\cdot}$, ^{81}Br, ^{37}Cl, ^{35}Cl, 7%], 533 [($M^{+\cdot}$, ^{79}Br, ^{37}Cl, ^{35}Cl, 20%], 531 [($M^{+\cdot}$, ^{79}Br, ^{35}Cl, ^{35}Cl, 15%], 366 [20], 196 [78].
HRMS (EI)	calcd for $C_{16}H_{12}NO_4SCl_4{}^{79}Br$ ($M^{+\cdot}$) 532.84190, found 532.83911.

4-Bromo-2-(4-methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester [139a]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) and DABCO (16.0 mg, 0.142 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-methoxybenzyl)-*N*-phenylmethylidene amine oxide **118c** (410 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 1 hour. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in

petroleum ether 40-60 °C) to give the title compound **139a** as yellow oil and an in separable 3:1 mixture of diastereoisomers (0.55 g, 0.92 mmol, 65%):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 3 H, Ar*H*), 7.48 – 7.39 (m, 3 H, Ar*H*), 7.27 – 7.23 (m, 2 H, Ar*H*), 6.89 (d, *J* = 8.7 Hz, 2 H, Ar*H*, minor), 6.82 (d, *J* = 8.8 Hz, 2 H, Ar*H*, major), 5.08 (d, *J* = 11.1 Hz, 1 H, OC*H*H, minor), 5.06 (d, *J* = 11.1 Hz, 1 H, OC*H*H, major), 4.67 (s, 1 H, NC*H*Ar, minor), 4.65 (s, 1 H, NC*H*Ar, major), 4.60 (d, *J* = 11.0, 1 H, OCH*H*, minor), 4.57 (d, *J* = 11.2, 1 H, OCH*H*, major), 4.16 (d, *J* = 14.5 Hz, 1 H, NC*H*HAr, minor), 4.10 (d, *J* = 14.3 Hz, 1 H, NC*H*HAr, major), 3.81 (s, 3 H, OCH_3, minor), 3.79 (s, 3 H, OCH_3, major), 3.71 (d, *J* = 14.5 Hz, 1 H, NCH*H*Ar, minor).

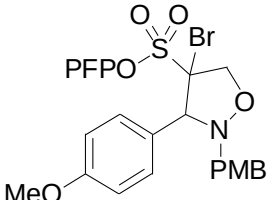
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (s), 134.5 (s), 130.5 (s), 129.7 (d), 128.6 (d), 125.8 (d), 113.9 (d), 83.1 (s), 77.9 (t), 74.9 (d), 59.0 (t), 55.3 (q).

IR (neat) 2943 (s, CH), 1611 (s), 1511 (s, C=C), 1393 (s, S=O), 1245 (s), 1176 (s), 980 (s) cm^{-1}.

LRMS (FAB) 618 [$(M+Na)^+$, ^{81}Br, 11%], 616 [$(M+Na)^+$, ^{79}Br, 11%], 314 [26], 176 [100].

HRMS (FAB) calcd for $C_{23}H_{17}{}^{79}BrF_5NNaO_5S$ $(M+Na)^+$ 615.9829, found 615.9817.

4-Bromo-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester [139b]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) and DABCO (16.0 mg, 0.142 mmol) was dissolved in PhMe (5 mL) and treated with *N*-

(4-methoxybenzyl)-*N*-(4-methoxyphenyl) methylidene amine oxide **118a** (410 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 1 hour. Solvent was removed in vacuo and the crude residue purified by flash chromatography (starting 9:1 petroleum ether 40-60 °C/Et_2O) to give the title compound **139b** a yellow oil as a single diastereoisomer (0.76 g, 1.22 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 7.26 – 7.21 (m, 2 H, Ar*H*), 6.98 (d, *J* = 7.7 Hz, 2 H, Ar*H*), 6.88 – 6.84 (m, 2 H, Ar*H*), 5.07 (d, *J* = 11.1 Hz, 1 H, OC*H*H), 4.61 (s, 1 H, NC*H*), 4.57 (d, *J* = 11.2 Hz, 1 H, OCH*H*), 4.10 (d, *J* = 14.3 Hz, 1 H, NC*H*H), 3.86 (s, 3 H, C*H*$_3$), 3.80 (s, 3 H, C*H*$_3$), 3.76 (d, *J* = 14.3 Hz, 1 H, NCH*H*).

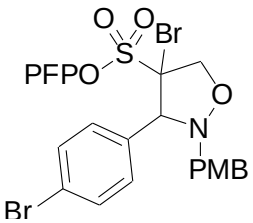
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5 (s), 159.3 (s), 131.3 (s), 130.5 (d), 129.3 (d), 127.9 (s), 114.2 (d), 113.7 (d), 83.6 (s), 77.8 (t), 74.7 (d), 58.9 (t), 55.2 (q).

IR (neat) 2943 (s, CH), 1611 (s), 1511 (s, C=C), 1393 (s, S=O), 1245 (s), 1176 (s), 980 (s) cm^{-1}.

LRMS (FAB) 649 [(M+Na)$^+$, ^{81}Br, 20%], 647 [(M+Na)$^+$, ^{79}Br, 18%], 329 [20], 176 [100].

HRMS (FAB) calcd for $C_{24}H_{19}NO_6SF_5{}^{79}BrNa$ (M+Na)$^+$ 646.99343, found 646.99188.

4-Bromo-3-(4-bromophenyl)-2-(4-methoxybenzyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester [139c]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) and DABCO (16.0 mg, 0.142 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-bromobenzyl)-*N*-(4-methoxyphenyl) methylidene amine oxide[81] (0.54 g, 1.70 mmol). The resulting suspension was stirred at reflux for 24 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **139c** a yellow oil as a single diastereoisomer (350 mg, 0.52 mmol, 37%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.44 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.24 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.10 (d, *J* = 11.2 Hz, 1 H, OC*H*H), 4.63 (s, 1 H, NC*H*Ar), 4.57 (d, *J* = 11.2 Hz, 1 H, OCH*H*), 4.11 (d, *J* = 14.3 Hz, 1 H, NC*H*HAr), 3.86 (d, *J* = 14.3, 1 H, NCH*H*Ar), 3.81 (s, 3 H, OC*H*$_3$).

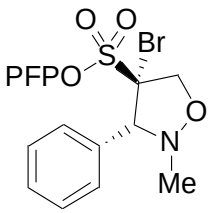
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0 (s), 159.3 (s), 132.9 (s), 132.5 (d), 130.9 (d), 129.1 (d), 127.3 (s), 123.9 (s), 113.7 (d), 82.7 (s), 77.8 (d), 74.1 (t), 59.0 (d), 55.2 (q).

IR (neat) 1611 (s), 1561 (s, C=C), 1386 (s, S=O), 1247 (s), 1191 (s), 998 (s) cm^{-1}.

LRMS (EI) 673 [$M^{+\cdot}$, ^{81}Br, ^{81}Br, 3%], 671 [$M^{+\cdot}$, ^{81}Br, ^{79}Br, 5%], 669 [$M^{+\cdot}$, ^{79}Br, ^{79}Br, 3%], 354 [54], 184 [70].

HRMS (EI) calcd for $C_{23}H_{16}NO_5SF_5{}^{79}Br_2$ ($M^{+\cdot}$) 670.90306, found 670.90470.

4-Bromo-2-methyl-3-phenyl-isoxazolidine-4-sulfonic acid pentafluoro phenyl ester [137a]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) and DABCO (16.0 mg, 0.142 mmol) was dissolved in PhMe (5 mL) and treated with *N*-methyl-*N*-phenylmethylidene amine oxide **114a** (230 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 2 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **137a** a white solid as a single diastereoisomer (490 mg, 1.00 mmol, 71%):

MP 88 – 90 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 5 H, Ar*H*), 5.12 (d, *J* = 11.1 Hz, 1 H, OC*H*H), 4.64 (d, *J* = 11.1 Hz, 1 H, OCH*H*), 4.41 (s, 1 H, NC*H*Ar), 2.78 (s, 3 H, NCH_3).

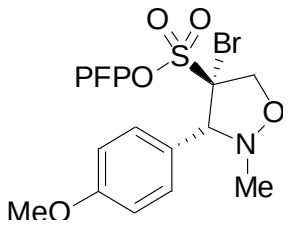
^{13}C NMR (150 MHz, $CDCl_3$) δ 137.1 (s), 130.0 (d), 129.6 (d), 83.5 (s), 78.1 (t), 77.7 (d), 43.2 (q).

IR (neat) 2878 (w), 1612 (s), 1561 (s, C=C), 1467 (s), 1384 (s, S=O), 1250 (s), 1181 (s), 994 (s) cm^1.

LRMS (EI) 489 [$M^{+\cdot}$, ^{81}Br, 20%], 487 [$M^{+\cdot}$, ^{79}Br, 18%], 354 [5], 184 [55], 160 [44], 134 [100].

HRMS (EI) calcd for $C_{16}H_{11}NO_4SF_5{}^{79}Br$ ($M^{+\cdot}$) 486.95068, found 486.94927.

4-Bromo-3-(4-methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester [137b]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) was dissolved in PhMe (5 mL) and treated with ***N***-(4-methoxyphenyl) methylidene-***N***-

methylamine oxide **114b** (230 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **137b** a colourless syrup as one single diastereoisomer (0.53 g, 1.02 mmol, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.93 (d, *J* = 8.9 Hz, 2 H, Ar*H*), 5.10 (d, *J* = 11.1 Hz, 1 H, OC*H*H), 4.60 (d, *J* = 11.1 Hz, 1 H, OCH*H*), 4.35 (s, 1 H, NC*H*Ar), 3.83 (s, 3 H, CH_3), 2.75 (s, 3 H, CH_3).

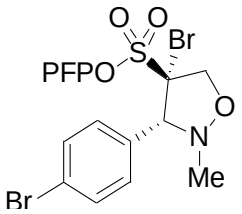
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5 (s), 131.1 (d), 125.3 (s), 113.8 (d), 84.0 (s), 78.0 (t), 77.6 (d), 55.3 (q), 43.1 (q).

IR (neat) 2878 (w), 1612 (s), 1561 (s, C=C), 1467 (s), 1384 (s, S=O), 1250 (s), 1181 (s), 994 (s) cm^{-1}.

LRMS (EI) 519 [$M^{+\cdot}$, ^{81}Br, 10%], 517 [$M^{+\cdot}$, ^{79}Br, 8%], 354 [10], 184 [50], 165 [100].

HRMS (EI) calcd for $C_{17}H_{13}NO_5SF_5{}^{79}Br$ ($M^{+\cdot}$) 516.96124, found 516.96194.

4-Bromo-3-(4-bromophenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [137d]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) was dissolved in PhMe (5 mL) and treated with ***N***-(4-bromophenyl) methylidene-***N***-methylamine oxide[81] (230 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title

compound **137d** a light yellow syrup as a single diastereoisomer (0.61 g, 1.08 mmol, 76%):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.33 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 5.09 (d, *J* = 11.1 Hz, 1 H, OC*H*H), 4.58 (d, *J* = 11.1 Hz, 1 H, OCH*H*), 4.35 (s, 1 H, NC*H*Ar), 2.76 (s, 3 H, CH_3).

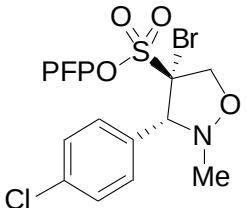
^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6 (s), 131.8 (d), 131.4 (d), 124.0 (s), 83.1 (s), 78.0 (t), 77.2 (d), 43.1 (q).

IR (neat) 2880 (w), 1561 (s, C=C), 1472 (s), 1388 (s, S=O), 1194 (s), 994 (s) cm^{-1}.

LRMS (EI) 567 [$M^{+\cdot}$, ^{81}Br, ^{81}Br, 63%], 565 [$M^{+\cdot}$, ^{81}Br, ^{79}Br, 65%], 563 [$M^{+\cdot}$, ^{79}Br, ^{79}Br, 63%], 240 [20], 213 [100], 165 [55].

HRMS (EI) calcd for $C_{16}H_{10}NO_4SF_5{}^{79}Br_2$ ($M^{+\cdot}$) 564.86120, found 564.86034.

4-Bromo-3-(4-chlorophenyl)-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [137c]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) was dissolved in PhMe (5 mL) and treated with ***N***-(4-chlorophenyl) methylidene-***N***-methylamine oxide[81] (290 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **137c** a light yellow syrup as a single diastereoisomer (0.61 g, 1.16 mmol, 82%):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 4 H, Ar*H*), 5.10 (d, *J* = 11.1 Hz, 1 H,

OC*H*H), 4.58 (d, *J* = 11.1 Hz, 1 H, OCH*H*), 4.37 (s, 1 H, NC*H*Ar), 2.76 (s, 3 H, CH_3).

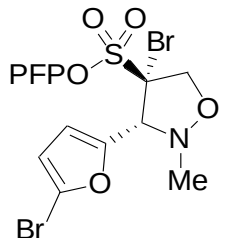
^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7 (s), 132.1 (s), 131.2 (d), 128.8 (d), 83.1 (s), 78.0 (t), 77.2 (d), 43.1 (q).

IR (neat) 2933 (w), 1517 (s, C=C), 1493 (s, C=C), 1383 (s, S=O), 1192 (s), 994 (s) cm^{-1}.

LRMS (EI) 523 [$M^{+\cdot}$, 15%], 525 [$M^{+\cdot}$, ^{81}Br, ^{37}Cl, 13%], 523 [$M^{+\cdot}$, ^{79}Br, ^{37}Br, 15%], 521 [$M^{+\cdot}$, ^{79}Br, ^{35}Cl, 13%], 352 [5], 276 [3], 169 [100].

HRMS (EI) calcd for $C_{16}H_{10}NO_4SF_5{}^{79}BrCl$ ($M^{+\cdot}$) 520.91171, found 520.91295.

4-Bromo-3-(5-bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenylester [137e]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(5-bromofuran-2-yl) methylidene-*N*-methylamine oxide[81] (350 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **137e** a light yellow syrup as a single diastereoisomer (350 mg, 0.63 mmol, 45%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, *J* = 3.4 Hz, 1 H, BrC*H*), 6.40 (d, *J* = 3.4 Hz, 1 H, CC*H*), 5.07 (d, *J* = 11.1 Hz, 1 H, OC*H*H), 4.59 (d, *J* = 11.1 Hz, 1 H, OCH*H*), 4.56 (s, 1 H, NC*H*), 2.86 (s, 3 H, NCH_3).

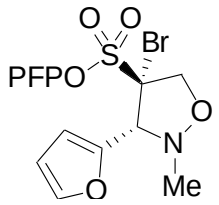
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2 (s), 123.9 (s), 115.1 (d), 112.6 (d), 81.2 (s), 77.8 (t), 72.9 (d), 43.5 (q).

IR (neat) 2927 (w), 1684 (w), 1516 (s, C=C), 1473 (s, C=C), 1396 (s, S=O), 1197 (s), 997 (s) cm^{-1}.

LRMS (EI) 557 [$M^{+\cdot}$, ^{81}Br, ^{81}Br, 13%], 555 [$M^{+\cdot}$, ^{81}Br, ^{79}Br, 15%], 553 [$M^{+\cdot}$, ^{79}Br, ^{79}Br, 13%], 205 [100].

HRMS (EI) calcd for $C_{14}H_8NO_5SF_5{}^{79}Br_2$ (M^+) 554.84046, found 554.84020.

4-Bromo-3-furan-2-yl-2-methyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [137f]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) was dissolved in PhMe (5 mL) and treated with *N*-furan-2-ylmethylidene-*N*-methylamine oxide **114e** (210 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **137f** a light yellow syrup as a single diastereoisomer (250 mg, 0.52 mmol, 36%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 0.8, 1.8 Hz, 1 H, OC*H*), 6.56 (d, *J* = 3.3 Hz, 1 H, C*H*), 6.46 (dd, *J* = 1.8, 3.3 Hz, 1 H, CC*H*), 5.08 (m, 1 H, OC*H*H), 4.62 (m, 2 H, OCH*H*, NC*H*), 2.85 (s, 3 H, C*H*$_3$).

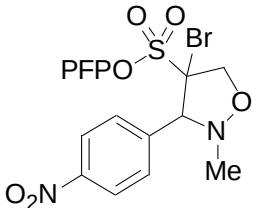
^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6 (s), 144.0 (d), 112.5 (d), 110.7 (d), 81.7 (s), 77.9 (t), 73.1 (d), 43.5 (q).

IR (neat) 2976 (w), 1515 (s, C=C), 1473 (s, C=C), 1390 (s, S=O), 1197 (s), 993 (s) cm^{-1}.

LRMS (CI) 480 [$(M+H)^+$, ^{81}Br, 7%], 478 [$(M+H)^{+\cdot}$, ^{79}Br, 5%], 355 [35].

HRMS (CI) calcd for $C_{14}H_{10}NO_5SF_5{}^{79}Br$ $(M+H)^+$ 477.93832, found 477.93608.

4-Bromo-2-methyl-3-(4-nitrophenyl)-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [137g]



1-Bromoethenesulfonic acid pentafluorophenyl ester **126** (0.50 g, 1.42 mmol) was dissolved in PhMe (5 mL) and treated with *N*-methyl-*N*-(4-nitrophenyl) methylidene amine oxide **114c** (310 mg, 1.70 mmol). The resulting suspension was stirred at reflux for 30 mins. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **137g** a light yellow syrup in an inseparable 7:1 mixture of diastereoisomers (350 mg, 0.66 mmol, 46%):

^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2 H, Ar*H*, major), 8.24 (d, *J* = 8.6 Hz, 2 H, Ar*H*, minor), 7.77 (d, *J* = 8.6 Hz, 2 H, Ar*H*, major), 7.68 (d, *J* = 8.7 Hz, 2 H, Ar*H*, minor), 5.12 (d, *J* = 11.1 Hz, 1 H, OC*H*H, major), 5.11 (d, *J* = 11.1 Hz, 1 H, OC*H*H, minor), 4.66 (d, *J* = 11.0 Hz, 1 H, OCH*H*, minor), 4.61 (d, *J* = 11.2 Hz, 1 H, OCH*H*, major), 4.57 (s, 1 H, NC*H*, minor), 4.51 (s, 1 H, NC*H*, major), 2.80 (s, 3 H, C*H*$_3$, major), 2.77 (s, 3 H, C*H*$_3$, minor).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7 (s), 141.9 (s), 130.9 (d), 123.6 (d),

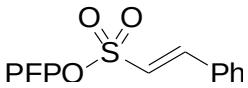
82.5 (s), 78.1 (t), 76.9 (d), 43.2 (q).

IR (neat) 2254 (w), 1609 (w), 1519 (s, C=C), 1390 (s, NO_2), 1350 (s, S=O), 1196 (s), 999 (s) cm^{-1}.

LRMS (EI) 532 [$M^{+\cdot}$ 15 %], 534 [$M^{+\cdot}$, ^{81}Br, 13%], 532 [$M^{+\cdot}$, ^{79}Br, 15%], 354 [15], 184 [100].

HRMS (EI) calcd for $C_{16}H_{10}N_2O_6SF_5{}^{79}Br$ ($M^{+\cdot}$) 531.93576, found 531.93529.

2-Phenyl-ethenesulfonic acid pentafluorophenyl ester [122]



Trans-β-styrene sulfonyl chloride **121** (5.50 g, 27.2 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78 °C. Pentafluorophenol (5.00 g, 27.2 mol) and NEt_3 (8.7 mL, 62.5 mmol) were pre-mixed in CH_2Cl_2 (10 mL) and added dropwise to the stirred solution of trans-β-styrene sulfonyl chloride. The reaction was stirred for 1 hour at 20 °C after which it was diluted with Et_2O (50 mL) and washed with 2M HCl (50 mL) and sat. $NaHCO_3$ (50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to yield the title compound as a white solid **122** (7.60 g, 21.6 mmol, 80%);

MP 96 – 98 °C

^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.4 Hz, 1 H, C*H*), 7.58 – 7.44 (m, 5 H, Ar*H*), 6.95 (d, *J* = 15.4 Hz, 1 H, C*H*).

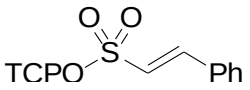
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6 (s), 148.1 (d), 132.5 (d), 131.3 (s), 129.5 (d), 129.0 (d), 119.8 (d).

IR (neat) 2921 (w), 2853 (w), 1613 (s, C=C), 1518 (s, C=C), 1394 (s, S=O), 1175 (s) cm^{-1}.

LRMS (EI) 350 [$M^{+\cdot}$, 7%], 167 [60], 103 [100].

HRMS (EI) calcd for $C_{14}H_7O_3SF_5$ (M^+) 350.00306, found 350.00341.

2-Phenyl-ethenesulfonic acid 2,4,6-trichlorophenyl ester [123]



Trans-β-styrene sulfonyl chloride **121** (2.80 g, 13.8 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C. 2,4,6 Trichlorophenol (2.72 g, 13.8 mmol) and NEt_3 (4.4 mL, 31.8 mmol) were pre-mixed in CH_2Cl_2 (10 mL) and added dropwise to the stirred solution of trans-β-styrene sulfonyl chloride. The reaction was stirred for 1 hour after which it was diluted with Et_2O (50 mL) and washed with 2M HCl (50 mL) and sat. $NaHCO_3$ (50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to yield the title compound **123** as a white solid (4.30 g, 11.9 mmol, 86%);

MP 126 – 128 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.5 Hz, 1 H, C*H*), 7.52 – 7.48 (m, 5 H, Ar*H*), 7.40 (s, 2 H, Ar*H*), 6.95 (d, *J* = 15.4 Hz, 1 H, C*H*).

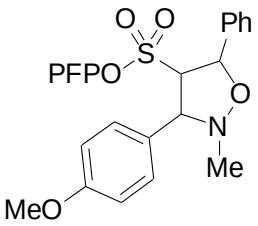
^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1 (d), 142. 3 (s), 133.1 (s), 132.1 (d), 131.7 (s), 129.4 (d), 129.3 (d), 128.9 (d), 122.4 (d).

IR (neat) 3081 (w), 1613 (s, C=C), 1561 (s, C=C), 1440 (s), 1366 (s, S=O), 1227 (s), 1169 (s) cm^{-1}.

LRMS (EI) 364 [$M^{+\cdot}$, ^{37}Cl, 7%], 362 [$M^{+\cdot}$, ^{35}Cl, 5%], 198 [5], 167 [80], 103 [100].

HRMS (EI) calcd for $C_{14}H_9O_3SCl_3$ ($M^{+\cdot}$) 361.93325, found 361.93428.

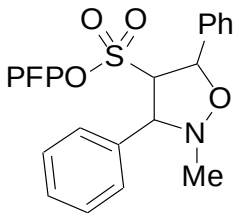
3-(4-Methoxyphenyl)-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124a]



2-Phenylethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-methoxyphenyl) methylidene-*N*-methylamine oxide **114b** (280 mg, 1.71 mmol). The resulting suspension was stirred at reflux for 4 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the title compound **124a** a clear syrup as a single diastereoisomer (390 mg, 0.76 mmol, 53%);

^{1}H NMR	(400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 7.52 – 7.41 (m, 2 H, Ar*H*), 7.40 – 7.33 (m, 1 H, Ar*H*), 7.31 – 7.21 (m, 2 H, Ar*H*), 6.94 – 6.82 (m, 2 H, Ar*H*), 5.78 (d, *J* = 4.1 Hz, 1 H, OC*H*Ar), 4.44 (dd, *J* = 4.2, 7.7 Hz, 1 H, SO_2C*H*), 4.25 (d, *J* = 7.7 Hz, 1 H, NC*H*), 3.79 (s, 3 H, CH_3), 2.77 (s, 3H, CH_3).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 172.1 (s), 160.2 (s), 129.4 (d), 128.9 (d), 128.3 (d), 127.0 (s), 125.9 (d), 114.5 (d), 81.1 (d), 78.7 (d), 75.0 (d), 42.8 (q), 31.0 (q).
IR (neat)	2960 (w), 1612 (w), 1515 (s, C=C), 1458 (w), 1384 (s, S=O), 1250 (s), 1176 (s), 994 (s) cm^{-1}.
LRMS (EI)	515 [$M^{+\cdot}$, 10%], 165 [100], 103 [35].
HRMS (EI)	calcd for $C_{23}H_{18}F_5O_5NS$ ($M^{+\cdot}$) 515.08203, found 515.08055.

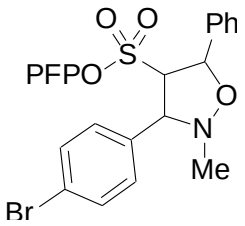
2-Methyl-3,5-diphenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124b]



2-Phenyl-ethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-methyl-*N*-phenylmethylidene amine oxide **114a** (290 mg, 2.14 mmol). The resulting suspension was stirred at reflux for 5 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **124b** a clear syrup as a single diastereoisomer (420 mg, 0.87 mmol, 61%);

^{1}H NMR	(500 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2 H, Ar*H*), 7.49 – 7.40 (m, 2 H, Ar*H*), 7.39 – 7.29 (m, 6 H, Ar*H*), 5.79 (d, *J* = 4.2 Hz, 1 H, OC*H*Ar), 4.47 (dd, *J* = 4.2, 7.6 Hz, 1 H, SO_2C*H*), 4.30 (d, *J* = 7.5 Hz, 1 H, NC*H*), 2.79 (s, 3 H, CH_3).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 138.8 (s), 135.4 (s), 129.2 (d), 129.1 (d), 128.9 (d), 128.3 (d), 125.9 (d), 125.8 (d), 81.2 (d), 78.9 (d), 75.4 (d), 42.9 (q).
IR (neat)	3035 (w), 2873 (w), 1516 (s, C=C), 1456 (w), 1384 (s, S=O), 1183 (s), 994 (s) cm^{-1}.
LRMS (EI)	485 [$M^{+\cdot}$, 25%], 167 [30], 135 [100], 103 [40].
HRMS (EI)	calcd for $C_{22}H_{16}F_5O_4NS$ ($M^{+\cdot}$) 485.0715, found 485.0705.

3-(4-Bromo-phenyl)-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124c]



2-Phenyl-ethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-bromophenyl) methylidene-*N*-methylamine oxide[81] (1.50 g, 7.14 mmol). The resulting suspension was stirred at reflux for 4 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **124c** a clear syrup as a single diastereoisomer (300 mg, 0.54 mmol, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 2 H, Ar*H*), 7.55 – 7.34 (m, 5 H, Ar*H*), 7.34 – 7.23 (m, 2 H, Ar*H*), 5.83 (d, *J* = 4.2 Hz, 1 H, OC*H*Ar), 4.45 (dd, *J* = 4.3, 7.5 Hz, 1 H, SO_2C*H*), 4.34 (d, *J* = 7.5 Hz, 1 H, NC*H*), 2.84 (s, 3 H, CH_3).

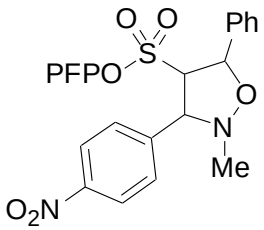
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8 (s), 134.7 (s), 132.4 (d), 129.8 (d), 129.0 (d), 128.4 (d), 125.8 (d), 123.3 (s), 81.1 (d), 79.0 (d), 74.6 (d), 42.9 (q).

IR (neat) 2921 (w), 1517 (s, C=C), 1488 (w), 1383 (s, S=O), 1183 (s), 994 (s) cm^{-1}.

LRMS (EI) 563 [$M^{+\cdot}$, 21%], 213 [65], 167 [85].

HRMS (EI) calcd for $C_{22}H_{15}BrF_5O_4NS$ ($M^{+\cdot}$) 562.98198, found 562.98286.

2-Methyl-3-(4-nitrophenyl)-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124f]



2-Phenylethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-nitrophenyl) methylidene-*N*-methylamine oxide **114c** (1.20 g, 7.14 mmol). The resulting suspension was stirred at reflux for 18 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **124f** as a light yellow syrup as a single distereoisomer (210 mg, 0.39 mmol, 27%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 – 8.18 (m, 2 H, Ar*H*), 7.61 – 7.56 (m, 2 H, Ar*H*), 7.54 (d, *J* = 7.3 Hz, 2 H, Ar*H*), 7.46 – 7.40 (m, 2 H, Ar*H*), 7.40 – 7.34 (m, 1 H, Ar*H*), 5.83 (d, *J* = 4.4 Hz, 1 H, OC*H*Ar), 4.48 (d, *J* = 7.2 Hz, 1 H, NC*H*), 4.39 (dd, *J* = 4.4, 7.2 Hz, 1 H, SO_2C*H*), 2.85 (s, 3 H, CH_3).

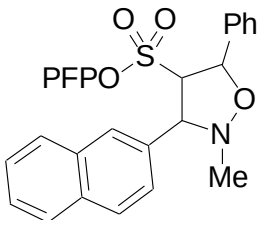
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6 (s), 143.4 (s), 138.9 (s), 129.1 (d), 129.0 (d), 128.7 (d), 125.9 (d), 124.4 (d), 80.7 (d), 79.7 (d), 74.2 (d), 43.4 (q).

IR (neat) 2972 (w), 1517 (s, C=C), 1376 (s, NO_2), 1355 (S=O), 1183 (s), 993 (s) cm^{-1}.

LRMS (EI) 530 [$M^{+\cdot}$, 21%], 180 [100], 103 [50].

HRMS (EI) calcd for $C_{22}H_{15}F_5O_6N_2S$ ($M^{+\cdot}$) 530.05655, found 530.05785.

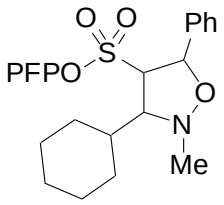
2-Methyl-3-naphthalen-2-yl-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124g]



2-Phenylethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-methyl-*N*-naphthalen-2-ylmethylidene amine oxide **114d** (0.53 g, 2.86 mmol). The resulting suspension was stirred at 80 °C for 48 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **124g** a clear syrup as a single diastereoisomer (490 mg, 0.92 mmol, 65%):

^{1}H NMR	(500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.3 Hz, 1 H, Ar*H*), 7.85 – 7.78 (m, 3 H, Ar*H*), 7.66 (d, *J* = 7.3 Hz, 2 H, Ar*H*), 7.57 – 7.43 (m, 4 H, Ar*H*), 7.40 – 7.38 (m, 2 H, Ar*H*), 5.86 (d, *J* = 4.2 Hz, 1 H, OC*H*Ar), 4.59 (dd, *J* = 4.2, 7.5 Hz, 1 H, SO_2C*H*), 4.50 (d, *J* = 7.5 Hz, 1 H, NC*H*), 2.84 (s, 3 H, CH_3).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 140.0 (s), 136.9 (s), 133.6 (s), 133.3 (s), 132.7 (s), 129.2 (d), 129.0 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.8 (d), 126.8 (d), 126.6 (d), 125.9 (d), 124.6 (d), 80.9 (d), 79.0 (d), 75.6 (d), 43.1 (q).
IR (neat)	3056 (w), 2873 (w), 1516 (s, C=C), 1470 (w), 1381 (s, S=O), 1183 (s), 992 (s) cm^{-1}.
LRMS (EI)	535 [$M^{+\cdot}$, 35%], 243 [20], 185 [95], 167 [85].
HRMS (EI)	calcd for $C_{26}H_{18}O_4NSF_5$ ($M^{+\cdot}$) 535.08712, found 535.08682.

3-Cyclohexyl-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124e]



2-Phenylethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-cyclohexylmethylidene-*N*-methylamine oxide[81] (400 mg, 2.86 mmol). The resulting suspension was stirred at reflux for 4 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **124e** a clear syrup as a single diastereoisomer (230 mg, 0.66 mmol, 33%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H, Ar*H*), 7.45 – 7.33 (m, 3 H, Ar*H*), 5.82 (d, *J* = 7.3 Hz, 1 H, C*H*Ar), 4.22 (dd, *J* = 4.5, 7.3 Hz, 1 H, SO_2C*H*), 3.48 (dd, *J* = 4.5, 6.6 Hz, 1 H, NC*H*), 2.99 (s, 3 H, C*H*$_3$), 1.90 – 1.58 (m, 6 H, cyclohexyl-*H*), 1.20 (m, 5 H, cyclohexyl-*H*).

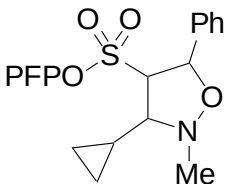
^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (s), 129.2 (d), 128.9 (d), 127.2 (d), 80.2 (d), 75.6 (d), 75.6 (d), 45.5 (q), 30.0 (t), 29.5 (t), 26.2 (t), 26.1 (s), 26.0 (t).

IR (neat) 2928 (s, CH), 2855 (s, CH), 1516 (s, C=C), 1450 (s), 1384 (s, S=O), 1182 (s), 998 (s) cm^{-1}.

LRMS (EI) 491 [$M^{+\cdot}$, 20%], 408 [100].

HRMS (EI) calcd for $C_{22}H_{22}O_4NSF_5$ ($M^{+\cdot}$) 491.11842, found 491.11943.

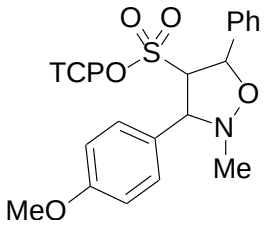
3-Cyclopropyl-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [124d]



2-Phenylethenesulfonic acid pentafluorophenyl ester **122** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-cyclopropylmethylidene-*N*-methylamine oxide **114f** (280 mg, 2.86 mmol). The resulting suspension was stirred at 80 °C for 18 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **124d** a clear syrup as a single diastereoisomer (140 mg, 0.31 mmol, 22%).

^{1}H NMR	(500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.4 Hz, 2 H, Ar*H*), 7.43 – 7.31 (m, 3 H, Ar*H*), 5.65 (s, 1 H, C*H*Ar), 4.37 (t, *J* = 5.4 Hz, 1 H, SO_2C*H*), 2.98 (s, 3 H, CH_3), 1.18 (m, 2 H, cyclopropyl-*H*), 0.77 – 0.45 (m, 4 H, cyclopropyl-*H*).
^{13}C NMR	(150 MHz, $CDCl_3$) δ 129.2 (d), 128.8 (d), 127.2 (d), 80.2 (d), 75.6 (d), 75.6 (d), 45.5 (q), 30.0 (t), 29.5 (t), 14.1 (d), 4.4 (t), 2.3 (t).
IR (neat)	1516 (s, C=C), 1470 (s), 1381 (s,S=O), 1183 (s), 992 (s) cm^{-1}.
LRMS (EI)	449 [$M^{+\cdot}$, 20%], 184 [100].
HRMS (EI)	calcd for $C_{19}H_{16}O_4NSF_5$ ($M^{+\cdot}$) 449.07147, found 449.07247.

3-(4-Methoxyphenyl)-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [125a]



2-Phenylethenesulfonic acid 2,4,6-trichlorophenyl ester **123** (0.50 g, 1.38 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-methoxyphenyl) methylidene-*N*-methylamine oxide **114b** (450 mg, 2.75 mmol). The resulting suspension was stirred at 80 °C for 48 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **125a** a clear syrup as a single stereoisomer (340 mg, 0.64 mmol, 46%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 2 H, Ar*H*), 7.46 – 7.39 (m, 2 H, Ar*H*), 7.38 – 7.28 (m, 5 H, Ar*H*), 6.90 – 6.81 (m, 2 H, Ar*H*), 5.84 (d, *J* = 4.3 Hz, 1 H, OC*H*Ar), 4.63 (dd, *J* = 4.3, 7.6 Hz, 1 H, SO_2C*H*), 4.33 (d, *J* = 7.5 Hz, 1 H, NC*H*), 3.79 (s, 3 H, CH_3), 2.80 (s, 3 H, CH_3).

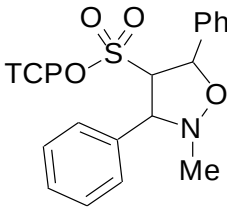
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0 (s), 141.5 (s), 133.2 (s), 130.7 (s), 129.5 (d), 129.2 (d), 128.8 (d), 128.1 (d), 127.5 (d), 126.1 (d), 114.3 (d), 81.7 (d), 79.1 (d), 75.1 (d), 55.3 (q), 42.8 (q).

IR (neat) 2964 (w), 1612 (s, C=C), 1513 (s, C=C), 1441 (s), 1384 (s, S=O), 1249 (s), 1174 (s), 1029 (s) cm^{-1}.

LRMS (EI) 529 [$M^{+\cdot}$, ^{37}Cl, 10%], 527 [$M^{+\cdot}$, ^{35}Cl, 8%], 165 [100].

HRMS (EI) calcd for $C_{23}H_{20}O_5NSCl_3$ ($M^{+\cdot}$) 527.01223, found 527.01345.

2-Methyl-3,5-diphenyl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [125b]



2-Phenylethenesulfonic acid 2,4,6-trichlorophenyl ester **123** (0.50 g, 1.38 mmol) was dissolved in PhMe (5 mL) and treated with *N*-methyl-*N*-phenylmethylidene amine oxide **114a** (370 mg, 2.75 mmol). The resulting suspension was stirred at 80 °C for 48 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **125b** a clear syrup as a single diastereoisomer (440 mg, 0.89 mmol, 65%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2 H, Ar*H*), 7.48 – 7.30 (m, 10 H, Ar*H*), 5.86 (d, *J* = 4.3 Hz, 1 H, OC*H*Ar), 4.66 (dd, *J* = 4.3, 7.4 Hz, 1 H, SO_2C*H*), 4.40 (d, *J* = 7.4 Hz, 1 H, NC*H*), 2.83 (s, 3 H, CH_3).

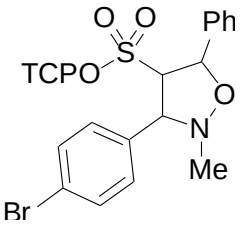
^{13}C NMR (125 MHz, $CDCl_3$) δ 141.53 (s), 136.03 (s), 133.30 (s), 130.76 (s), 129.21 (d), 129.01 (d), 128.94 (d), 128.85 (d), 128.29 (d), 128.19 (d), 126.14 (d), 81.94 (d), 79.25 (d), 75.45 (d), 43.03 (q).

IR (neat) 3078 (w), 2873 (w), 1561 (s, C=C), 1441 (s), 1385 (s, S=O), 1227 (s), 1175 (s), 1027 (w) cm^{-1}.

LRMS (EI) 499 [$M^{+\cdot}$, ^{37}Cl, 10%], 497 [$M^{+\cdot}$, ^{35}Cl, 8%], 196 [100].

HRMS (EI) calcd for $C_{22}H_{18}O_4NSCl_3$ ($M^{+\cdot}$) 497.00166, found 497.00207.

3-(4-Bromophenyl)-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid 2,4,6-trichlorophenyl ester [125c]



2-Phenylethenesulfonic acid 2,4,6-trichlorophenyl ester **123** (0.50 g, 1.43 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-bromophenyl) methylidene-*N*-methylamine oxide[81] (0.59 g, 2.75 mmol). The resulting suspension was stirred at 80 °C for 48 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **125c** a clear syrup as a single stereoisomer (200 mg, 0.35 mmol, 25%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2 H, Ar*H*), 7.50 – 7.39 (m, 4 H, Ar*H*), 7.38 – 7.32 (m, 3 H, Ar*H*), 7.31 – 7.25 (m, 3 H, Ar*H*), 5.85 (d, *J* = 4.4 Hz, 1 H, OC*H*Ar), 4.66 (dd, *J* = 4.4, 7.3 Hz, 1 H, SO_2C*H*), 4.38 (d, *J* = 7.3 Hz, 1 H, NC*H*), 2.83 (s, 3 H, CH_3).

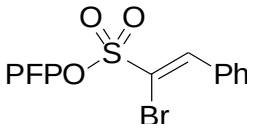
^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5 (s), 136.0 (s), 133.3 (s), 130.8 (s), 129.2 (d), 129.0 (d), 128.9 (d), 128.8 (d), 128.3 (d), 128.2 (d), 126.1 (d), 81.9 (d), 79.2 (d), 75.4 (d), 43.0 (q).

IR (neat) 3080 (w), 1561 (s, C=C), 1441 (s), 1385 (s, S=O), 1227 (s), 1176 (s), 906 (w) cm^{-1}.

LRMS (EI) 575 [$M^{+\cdot}$, 10%], 577 [$M^{+\cdot}$, ^{81}Br, ^{37}Cl, 8%], 575 [$M^{+\cdot}$, ^{79}Br, ^{37}Cl, 10%], 573 [$M^{+\cdot}$, ^{79}Br, ^{35}Cl, 8%], 213 [100].

HRMS (EI) calcd for $C_{22}H_{17}O_4NS^{79}BrCl_3$ ($M^{+\cdot}$) 574.91218, found 574.91124.

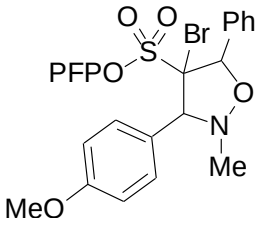
1-Bromo-2-phenylethenesulfonic acid pentafluorophenyl ester [142]



Bromine (5.9 mL, 114.2 mmol) in $CHCl_3$ (30 mL) was added dropwise over a period of 10 minutes to a stirring solution of 2-Phenylethenesulfonic acid pentafluorophenyl ester **122** (4.00 g, 11.4 mmol) in $CHCl_3$ (70 mL). After addition, the reaction mixture was heated at reflux for 4 hours, followed by 40 hours at 20 °C. The solvent was removed in vacuo and the crude oil remaining resuspended in CH_2Cl_2 (100 mL). To this stirring solution was added NEt_3 (3.2 mL, 22.8 mmol) and the reaction stirred at 20 °C for 3 hrs. The reaction mixture was washed with 2M HCl (100 mL), the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10-100% Et_2O in petroleum ether 40-60 °C) to give the titled compound **142** as a white solid (4.20 g, 9.4 mmol, 83%);

MP	64 – 66 °C
^{1}H NMR	(400 MHz, $CDCl_3$) δ 8.19 (s, 1 H, C*H*), 7.94 – 7.80 (m, 2 H, Ar*H*), 7.63 – 7.44 (m, 3 H, Ar*H*).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 143.8 (d), 132.2 (s), 131.1 (d), 130.6 (d), 129.0 (d), 112.6 (s).
IR (neat)	3080 (w), 1561 (s, C=C), 1441 (s), 1385 (s, S=O), 1227 (s), 1176 (s), 906 (w) cm^{-1}.
LRMS (EI)	430 [$M^{+\cdot}$, ^{81}Br, 10%], 428 [$M^{+\cdot}$, ^{79}Br, 8%], 245 [25], 183 [45].
HRMS (EI)	calcd for $C_{14}H_6O_3S^{79}BrF_5$ ($M^{+\cdot}$) 427.91357, found 427.91237.

4-Bromo-3-(4-methoxy-phenyl)-2-methyl-5-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester [143]



1-Bromo-2-phenyl-ethenesulfonic acid pentafluorophenyl ester **142** (0.50 g, 1.12 mmol) was dissolved in PhMe (5 mL) and treated with *N*-(4-methoxyphenyl) methylidene-*N*-methylamine oxide **114b** (0.93 g, 5.61 mmol). The resulting suspension was stirred at 50 °C for 48 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (chloroform) to give the title compound **143** a clear syrup as a single diastereoisomer (20 mg, 0.034 mmol, 3%):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 2 H, Ar*H*), 7.46 – 7.33 (m, 5 H, Ar*H*), 6.93 – 6.87 (m, 2 H, Ar*H*), 6.10 (s, 1 H, OC*H*), 4.71 (s, 1 H, NC*H*), 3.82 (s, 3 H, CH_3), 2.86 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5 (s), 136.0 (s), 133.3 (s), 130.7 (s), 129.2 (d), 129.0 (d), 128.9 (d), 128.8 (d), 128.2 (d), 128.1 (d), 126.1 (d), 81.9 (s), 79.2 (d), 75.4 (d), 55.3 (q), 43.0 (q).

IR (neat) 3080 (w), 1561 (s, C=C), 1441 (s), 1385 (s, S=O), 1227 (s), 1176 (s), 906 (w) cm^{-1}.

LRMS (EI) 595 [$M^{+\cdot}$, ^{81}Br, 5%], 593 [$M^{+\cdot}$, ^{79}Br, 3%], 430 [15], 247 [35], 183 [75], 102 [100].

HRMS (EI) calcd for $C_{23}H_{17}O_5NS^{79}BrF_5$ ($M^{+\cdot}$) 592.99255, found 592.99341.

4.6 Crystal structure data for 4-Bromo-2-methyl-3-phenyl-isoxazolidine-4-sulfonic acid pentafluoro phenyl ester [118a]

Table 1. Crystal data and structure refinement for str0758.

Identification code	str0758
Chemical formula	$C_{16}H_{11}BrF_5NO_4S$
Formula weight	488.23
Temperature	150(2) K
Radiation, wavelength	MoK□, 0.71073 Å
Crystal system, space group	triclinic, P $\bar{1}$
Unit cell parameters	a = 7.1179(16) Å □ = 73.950(3)°
	b = 10.832(2) Å □ = 85.840(4)°
	c = 12.340(3) Å □ = 70.976(3)°
Cell volume	864.3(3) $Å^3$
Z	2
Calculated density	1.876 g/cm^3
Absorption coefficient □	2.576 mm^{-1}
F(000)	484
Crystal colour and size	colourless, 0.50 × 0.20 × 0.04 mm^3
Data collection method	Bruker SMART APEX CCD diffractometer
	□ rotation with narrow frames
□ range for data collection	2.30 to 28.31°

Index ranges h –9 to 9, k –14 to 14, l –15 to 16

Completeness to □ = 26.00° 96.7 %

Reflections collected 7291

Independent reflections 3911 (R_{int} = 0.0262)

Reflections with F^2>2□ 3436

Absorption correction semi-empirical from equivalents

Min. and max. transmission 0.3591 and 0.9040

Structure solution direct methods

Refinement method Full-matrix least-squares on F^2

Weighting parameters a, b 0.0669, 0.5665

Data / restraints / parameters 3911 / 0 / 253

Final R indices [F^2>2□] R1 = 0.0373, wR2 = 0.1065

R indices (all data) R1 = 0.0429, wR2 = 0.1154

Goodness-of-fit on F^2 1.069

Largest and mean shift/su 0.001 and 0.000

Largest diff. peak and hole 0.800 and –0.759 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for str0758. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x y z U_{eq}

Br(1)	1.16668(4)	0.66791(3)	0.61916(3)	0.02941(12)
S(1)	0.93804(10)	0.49763(7)	0.75672(6)	0.02657(17)
O(1)	0.7043(3)	0.5182(2)	0.77933(19)	0.0290(5)
O(2)	1.0139(3)	0.3907(2)	0.7031(2)	0.0369(5)
O(3)	1.0290(4)	0.4905(2)	0.8571(2)	0.0376(5)
O(4)	0.5860(3)	0.7458(2)	0.57224(17)	0.0251(4)
N(1)	0.6156(3)	0.8535(2)	0.6127(2)	0.0230(5)
F(1)	0.6776(3)	0.3906(2)	1.00299(15)	0.0344(4)
F(2)	0.5069(3)	0.1922(2)	1.06511(16)	0.0405(5)
F(3)	0.3790(3)	0.1074(2)	0.90613(18)	0.0427(5)
F(4)	0.4257(3)	0.2187(2)	0.68461(17)	0.0373(4)
F(5)	0.5927(3)	0.4177(2)	0.62192(15)	0.0355(4)
C(1)	0.6169(4)	0.3491(3)	0.9244(2)	0.0248(6)
C(2)	0.5294(4)	0.2481(3)	0.9563(2)	0.0269(6)
C(3)	0.4637(4)	0.2044(3)	0.8752(3)	0.0281(6)
C(4)	0.4859(4)	0.2614(3)	0.7626(3)	0.0264(6)
C(5)	0.5730(4)	0.3622(3)	0.7311(2)	0.0258(6)
C(6)	0.6384(4)	0.4073(3)	0.8112(2)	0.0235(6)
C(7)	0.9004(4)	0.6605(3)	0.6565(2)	0.0217(5)
C(8)	0.7838(4)	0.6750(3)	0.5509(2)	0.0259(6)

C(9)	0.4219(4)	0.9194(3)	0.6548(3)	0.0277(6)
C(10)	0.7639(4)	0.7772(3)	0.7057(2)	0.0199(5)
C(11)	0.8543(4)	0.8698(3)	0.7376(2)	0.0217(5)
C(12)	0.8602(4)	0.9904(3)	0.6625(2)	0.0254(6)
C(13)	0.9348(4)	1.0776(3)	0.6967(3)	0.0301(6)
C(14)	1.0040(4)	1.0448(3)	0.8069(3)	0.0311(7)
C(15)	1.0008(5)	0.9239(3)	0.8809(3)	0.0338(7)
C(16)	0.9244(4)	0.8371(3)	0.8478(3)	0.0273(6)

Table 3. Bond lengths [Å] and angles [°] for str0758.

Br(1)–C(7)	1.940(3)	S(1)–O(3)	1.411(3)
S(1)–O(2)	1.426(2)	S(1)–O(1)	1.619(2)
S(1)–C(7)	1.802(3)	O(1)–C(6)	1.378(3)
O(4)–C(8)	1.412(3)	O(4)–N(1)	1.467(3)
N(1)–C(9)	1.463(4)	N(1)–C(10)	1.481(3)
F(1)–C(1)	1.325(3)	F(2)–C(2)	1.333(3)
F(3)–C(3)	1.330(3)	F(4)–C(4)	1.326(3)
F(5)–C(5)	1.332(3)	C(1)–C(2)	1.382(4)
C(1)–C(6)	1.385(4)	C(2)–C(3)	1.386(4)
C(3)–C(4)	1.377(4)	C(4)–C(5)	1.378(4)

C(5)–C(6)	1.383(4)	C(7)–C(8)	1.539(4)
C(7)–C(10)	1.565(4)	C(10)–C(11)	1.500(4)
C(11)–C(12)	1.388(4)	C(11)–C(16)	1.393(4)
C(12)–C(13)	1.391(4)	C(13)–C(14)	1.391(5)
C(14)–C(15)	1.380(5)	C(15)–C(16)	1.388(4)

O(3)–S(1)–O(2)	119.90(15)	O(3)–S(1)–O(1)	108.53(14)
O(2)–S(1)–O(1)	107.99(13)	O(3)–S(1)–C(7)	111.09(14)
O(2)–S(1)–C(7)	110.98(14)	O(1)–S(1)–C(7)	95.48(12)
C(6)–O(1)–S(1)	119.98(18)	C(8)–O(4)–N(1)	100.85(19)
C(9)–N(1)–O(4)	104.8(2)	C(9)–N(1)–C(10)	111.7(2)
O(4)–N(1)–C(10)	102.98(19)	F(1)–C(1)–C(2)	119.4(3)
F(1)–C(1)–C(6)	120.5(3)	C(2)–C(1)–C(6)	120.1(3)
F(2)–C(2)–C(1)	120.5(3)	F(2)–C(2)–C(3)	119.4(3)
C(1)–C(2)–C(3)	120.1(3)	F(3)–C(3)–C(4)	120.0(3)
F(3)–C(3)–C(2)	120.0(3)	C(4)–C(3)–C(2)	120.0(3)
F(4)–C(4)–C(3)	120.2(3)	F(4)–C(4)–C(5)	120.1(3)
C(3)–C(4)–C(5)	119.7(3)	F(5)–C(5)–C(4)	119.4(3)
F(5)–C(5)–C(6)	119.7(3)	C(4)–C(5)–C(6)	120.9(3)
O(1)–C(6)–C(5)	120.6(3)	O(1)–C(6)–C(1)	119.9(3)
C(5)–C(6)–C(1)	119.2(3)	C(8)–C(7)–C(10)	103.2(2)

C(8)–C(7)–S(1)	111.82(19)	C(10)–C(7)–S(1)	110.98(18)
C(8)–C(7)–Br(1)	111.31(19)	C(10)–C(7)–Br(1)	115.26(18)
S(1)–C(7)–Br(1)	104.47(14)	O(4)–C(8)–C(7)	103.8(2)
N(1)–C(10)–C(11)	110.7(2)	N(1)–C(10)–C(7)	101.2(2)
C(11)–C(10)–C(7)	118.9(2)	C(12)–C(11)–C(16)	119.2(3)
C(12)–C(11)–C(10)	121.9(3)	C(16)–C(11)–C(10)	118.8(3)
C(11)–C(12)–C(13)	120.5(3)	C(14)–C(13)–C(12)	120.1(3)
C(15)–C(14)–C(13)	119.2(3)	C(14)–C(15)–C(16)	121.0(3)
C(15)–C(16)–C(11)	120.0(3)		

Table 4. Anisotropic displacement parameters ($Å^2$) for str0758. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	0.02202(16)	0.02796(18)	0.03648(18)	–0.00917(13)	0.00622(12)	–0.00640(12)
S(1)	0.0227(3)	0.0177(3)	0.0356(4)	–0.0057(3)	0.0013(3)	–0.0030(3)
O(1)	0.0230(10)	0.0170(10)	0.0450(12)	–0.0081(9)	0.0058(9)	–0.0051(8)
O(2)	0.0288(11)	0.0210(11)	0.0592(15)	–0.0161(10)	0.0073(10)	–0.0028(9)

O(3) 0.0368(12) 0.0326(13) 0.0353(12) 0.0016(10) –0.0066(10) –0.0076(10)

O(4) 0.0241(10) 0.0263(10) 0.0280(10) –0.0134(8) –0.0005(8) –0.0069(8)

N(1) 0.0228(11) 0.0189(11) 0.0278(11) –0.0078(9) –0.0040(9) –0.0049(9)

F(1) 0.0373(10) 0.0367(11) 0.0319(9) –0.0145(8) –0.0053(8) –0.0099(8)

F(2) 0.0436(11) 0.0473(12) 0.0273(9) 0.0011(8) 0.0040(8) –0.0199(10)

F(3) 0.0399(11) 0.0341(11) 0.0565(13) 0.0001(9) –0.0091(9) –0.0231(9)

F(4) 0.0350(10) 0.0348(10) 0.0440(11) –0.0208(9) –0.0113(8) –0.0027(8)

F(5) 0.0407(10) 0.0350(10) 0.0229(8) –0.0037(7) 0.0023(7) –0.0055(8)

C(1) 0.0249(13) 0.0216(14) 0.0273(14) –0.0075(11) –0.0038(11) –0.0050(11)

C(2) 0.0248(13) 0.0244(15) 0.0278(14) –0.0031(11) 0.0001(11) –0.0061(11)

C(3) 0.0233(13) 0.0208(14) 0.0376(16) –0.0038(12) –0.0034(12) –0.0061(11)

C(4) 0.0218(13) 0.0228(14) 0.0329(15) –0.0124(12) –0.0067(11) 0.0008(11)

C(5) 0.0253(13) 0.0201(14) 0.0255(13) –0.0056(11) –0.0014(11) 0.0014(11)

C(6) 0.0216(13) 0.0151(13) 0.0307(14) –0.0033(10) –0.0004(11) –0.0040(10)

C(7) 0.0203(12) 0.0180(13) 0.0268(13) –0.0072(10) 0.0033(10) –0.0058(10)

C(8) 0.0256(14) 0.0250(14) 0.0277(14) –0.0119(11) 0.0025(11) –0.0054(11)

C(9) 0.0229(13) 0.0259(15) 0.0322(15) –0.0101(12) –0.0034(11) –0.0023(11)

C(10) 0.0184(12) 0.0167(12) 0.0239(12) –0.0053(10) –0.0013(10) –0.0044(10)

C(11) 0.0166(11) 0.0191(13) 0.0289(13) –0.0090(11) 0.0000(10) –0.0028(10)

C(12) 0.0240(13) 0.0233(14) 0.0287(14) –0.0060(11) 0.0007(11) –0.0081(11)

C(13) 0.0262(14) 0.0237(15) 0.0437(17) –0.0142(13) 0.0037(13) –0.0087(12)

C(14) 0.0210(13) 0.0304(16) 0.0499(18) –0.0229(14) –0.0014(12) –0.0080(12)

C(15) 0.0321(16) 0.0321(17) 0.0374(16) –0.0156(14) –0.0099(13) –0.0028(13)

C(16) 0.0281(14) 0.0233(14) 0.0292(14) –0.0070(11) –0.0034(12) –0.0055(11)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for str0758.

	x	y	z	U
H(8A)	0.8331	0.7270	0.4822	0.031
H(8B)	0.7946	0.5851	0.5416	0.031
H(9A)	0.3279	0.9692	0.5912	0.042
H(9B)	0.4354	0.9826	0.6950	0.042
H(9C)	0.3725	0.8506	0.7064	0.042
H(10A)	0.6950	0.7366	0.7728	0.024
H(12A)	0.8129	1.0134	0.5871	0.030
H(13A)	0.9384	1.1599	0.6447	0.036
H(14A)	1.0530	1.1048	0.8309	0.037
H(15A)	1.0517	0.8998	0.9556	0.041
H(16A)	0.9200	0.7553	0.9002	0.033

Table 6. Torsion angles [°] for str0758.

O(3)–S(1)–O(1)–C(6)	–93.6(2)	O(2)–S(1)–O(1)–C(6)	37.8(3)
C(7)–S(1)–O(1)–C(6)	152.0(2)	C(8)–O(4)–N(1)–C(9)	–170.9(2)
C(8)–O(4)–N(1)–C(10)	–54.0(2)	F(1)–C(1)–C(2)–F(2)	–0.3(4)
C(6)–C(1)–C(2)–F(2)	–179.5(3)	F(1)–C(1)–C(2)–C(3)	179.5(3)

C(6)–C(1)–C(2)–C(3)	0.2(4)	F(2)–C(2)–C(3)–F(3)	0.0(4)
C(1)–C(2)–C(3)–F(3)	−179.8(3)	F(2)–C(2)–C(3)–C(4)	179.9(3)
C(1)–C(2)–C(3)–C(4)	0.2(5)	F(3)–C(3)–C(4)–F(4)	−0.9(4)
C(2)–C(3)–C(4)–F(4)	179.1(3)	F(3)–C(3)–C(4)–C(5)	179.7(3)
C(2)–C(3)–C(4)–C(5)	−0.2(4)	F(4)–C(4)–C(5)–F(5)	1.2(4)
C(3)–C(4)–C(5)–F(5)	−179.5(3)	F(4)–C(4)–C(5)–C(6)	−179.4(3)
C(3)–C(4)–C(5)–C(6)	−0.1(4)	S(1)–O(1)–C(6)–C(5)	−92.1(3)
S(1)–O(1)–C(6)–C(1)	94.9(3)	F(5)–C(5)–C(6)–O(1)	6.8(4)
C(4)–C(5)–C(6)–O(1)	−172.5(3)	F(5)–C(5)–C(6)–C(1)	179.9(2)
C(4)–C(5)–C(6)–C(1)	0.5(4)	F(1)–C(1)–C(6)–O(1)	−6.7(4)
C(2)–C(1)–C(6)–O(1)	172.5(3)	F(1)–C(1)–C(6)–C(5)	−179.8(3)
C(2)–C(1)–C(6)–C(5)	−0.6(4)	O(3)–S(1)–C(7)–C(8)	−174.68(19)
O(2)–S(1)–C(7)–C(8)	49.3(2)	O(1)–S(1)–C(7)–C(8)	−62.4(2)
O(3)–S(1)–C(7)–C(10)	−60.0(2)	O(2)–S(1)–C(7)–C(10)	163.95(19)
O(1)–S(1)–C(7)–C(10)	52.3(2)	O(3)–S(1)–C(7)–Br(1)	64.82(17)
O(2)–S(1)–C(7)–Br(1)	−71.23(16)	O(1)–S(1)–C(7)–Br(1)	177.10(13)
N(1)–O(4)–C(8)–C(7)	46.0(2)	C(10)–C(7)–C(8)–O(4)	−22.1(3)
S(1)–C(7)–C(8)–O(4)	97.2(2)	Br(1)–C(7)–C(8)–O(4)	−146.33(19)
C(9)–N(1)–C(10)–C(11)	−83.2(3)	O(4)–N(1)–C(10)–C(11)	164.8(2)
C(9)–N(1)–C(10)–C(7)	149.8(2)	O(4)–N(1)–C(10)–C(7)	37.8(2)
C(8)–C(7)–C(10)–N(1)	−10.0(3)	S(1)–C(7)–C(10)–N(1)	−129.92(19)
Br(1)–C(7)–C(10)–N(1)	111.6(2)	C(8)–C(7)–C(10)–C(11)	−131.4(3)
S(1)–C(7)–C(10)–C(11)	108.6(2)	Br(1)–C(7)–C(10)–C(11)	−9.8(3)
N(1)–C(10)–C(11)–C(12)	−24.4(3)	C(7)–C(10)–C(11)–C(12)	92.0(3)
N(1)–C(10)–C(11)–C(16)	152.0(2)	C(7)–C(10)–C(11)–C(16)	−91.5(3)
C(16)–C(11)–C(12)–C(13)	−0.1(4)	C(10)–C(11)–C(12)–C(13)	176.3(3)
C(11)–C(12)–C(13)–C(14)	−0.1(4)	C(12)–C(13)–C(14)–C(15)	1.1(4)
C(13)–C(14)–C(15)–C(16)	−1.9(5)	C(14)–C(15)–C(16)–C(11)	1.7(5)

C(12)–C(11)–C(16)–C(15)	−0.6(4)	C(10)–C(11)–C(16)–C(15)	−177.2(3)

Chapter 5 References

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